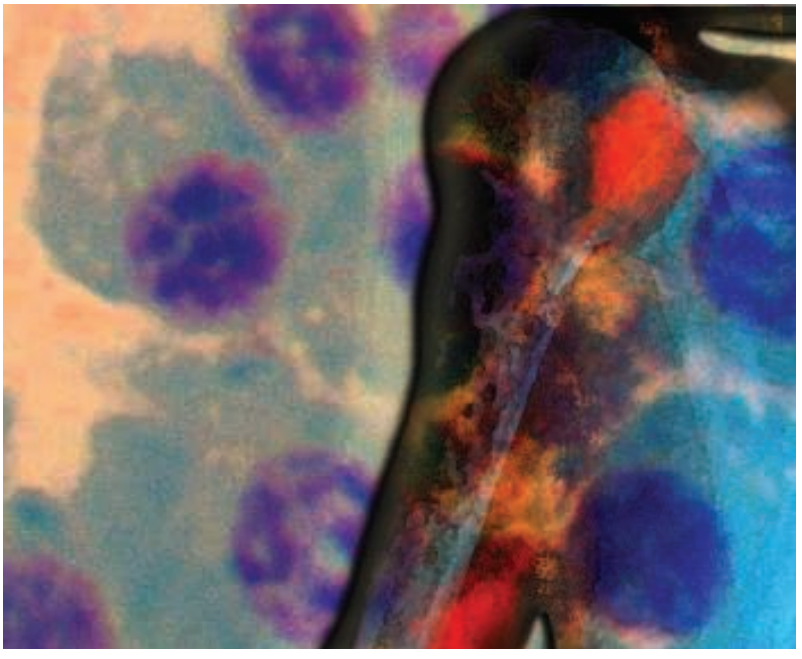
HOSPITAL PHYSICIAN®

Volume 5, Parts 1–3 2010

# HEMATOLOGY
## Board Review Manual



**Part 1: Disseminated Intravascular Coagulation**

**Part 2: Peripheral T-Cell Non-Hodgkin Lymphoma**

**Part 3: Hemoglobinopathies**

*The distribution of this publication is made possible through the financial support of Merck*

The Hospital Physician® Board Review Manuals are published by Turner White Communications, Inc., an independent medical publisher dedicated to serving the information and education needs of clinical trainees and practicing physicians.

HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

### STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

### PUBLISHING STAFF

**PRESIDENT, GROUP PUBLISHER**
Bruce M. White

**SENIOR EDITOR**
Robert Litchkofski

**EXECUTIVE VICE PRESIDENT**
Barbara T. White

**EXECUTIVE DIRECTOR OF OPERATIONS**
Jean M. Gaul

**PRODUCTION DIRECTOR**
Jeff White

**NOTE FROM THE PUBLISHER:**
This publication has been developed without involvement of or review by the American Board of Internal Medicine.

# Disseminated Intravascular Coagulation

**Series Editor:**
**Eric D. Jacobsen, MD**
*Instructor in Medicine, Harvard Medical School; Attending Physician, Dana-Farber Cancer Institute, Boston, MA*

**Contributor:**
**Thomas G. DeLoughery, MD, FACP**
*Professor of Medicine, Departments of Pathology and Pediatrics, Oregon Health Sciences University, Portland, OR*

## Table of Contents



**Cover Illustration by Kathryn K. Johnson**

# Disseminated Intravascular Coagulation

*Thomas G. DeLoughery, MD, FACP*

## INTRODUCTION

The process of coagulation is finely controlled at many levels to ensure the right amount of hemostasis at the right location. Broadly defined, disseminated intravascular coagulation (DIC) refers to any process that disrupts this fine tuning, leading to unregulated coagulation. Defined this way, DIC may be found in patients with a variety of diseases and can present with a spectrum of findings ranging from asymptomatic abnormal laboratory findings to florid bleeding or thrombosis. It is important to remember that DIC is always a consequence of an underlying pathological process and not a disease in and of itself. This manual reviews concepts common to all forms of DIC and discusses the more common disease states that lead to DIC.

## PATHOGENESIS

At the most basic level, DIC is the clinical manifestation of inappropriate thrombin activation.[1–4] Inappropriate thrombin activation can occur due to underlying conditions such as sepsis, obstetrical disasters, and trauma. The activation of thrombin leads to (1) conversion of fibrinogen to fibrin, (2) activation of platelets (and their consumption), (3) activation of factors V and VIII, (4) activation of protein C (and degradation of factors Va and VIIIa), (5) activation of endothelial cells, and (6) activation of fibrinolysis (**Table 1**).

Conversion of fibrinogen to fibrin leads to formation of fibrin monomers and excessive thrombus formation. These thrombi are rapidly dissolved by excessive fibrinolysis in most patients, but in certain clinical situations, especially cancer, excessive thrombosis will occur. In patients with cancer, this is most often a deep venous thrombosis, and rarely patients may have severe DIC with multiple arterial and venous thromboses, especially patients with pancreatic cancer. Nonbacterial thrombotic endocarditis can also be seen in these patients.

Because thrombin is the most potent physiologic activator of platelets, there is increased activation of platelets in DIC. These activated platelets are consumed, resulting in thrombocytopenia. Platelet dysfunction is also present. Platelets that have been activated and have released their contents but still circulate are known as “exhausted” platelets; these patients can no longer function to support coagulation. The fibrin degradation products (FDP) in DIC can also bind to GP IIb/IIIa and further inhibit platelet aggregation.

**Copyright 2010, Turner White Communications, Inc., Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications. The preparation and distribution of this publication are supported by sponsorship subject to written agreements that stipulate and ensure the editorial independence of Turner White Communications. Turner White Communications retains full control over the design and production of all published materials, including selection of topics and preparation of editorial content. The authors are solely responsible for substantive content. Statements expressed reflect the views of the authors and not necessarily the opinions or policies of Turner White Communications. Turner White Communications accepts no responsibility for statements made by authors and will not be liable for any errors of omission or inaccuracies. Information contained within this publication should not be used as a substitute for clinical judgment.**

**Table 1.** Consequences of Excessive Thrombin Generation

| | | |
|---|---|---|
| Conversion of fibrinogen to fibrin | → | Thrombosis and depletion of fibrinogen |
| Activation of platelets | → | Thrombocytopenia |
| Activation of factors V, VIII, XI, XIII | → | Thrombosis and depletion of coagulation factors |
| Activation of protein C | → | Depletion of factors V and VIII and eventually protein C |
| Activation of endothelial cells | → | Expression of tissue factor |
| Activation of fibrinolysis | → | Lysis of thrombi and depletion of fibrinogen |

Activation of factors V, VIII, XI, and XIII can promote thrombosis, but they are then rapidly cleared by antithrombin (XI) or activated protein C (V and VIII) or by binding to the fibrin clot (XIII). This can lead to depletion of all the prothrombotic clotting factors and antithrombin, resulting in both thrombosis and bleeding.

Activation of protein C further promotes degradation of factors Va and VIIIa, enhances fibrinolysis, and decreases protein C levels. Activation of endothelial cells, especially in the skin, may lead to thrombosis. Purpura fulminans also may develop in certain patients, especially those with meningococcemia. Endothelial damage will downregulate thrombomodulin, preventing activation of protein C and leading to further reductions in levels of activated protein C.[5]

Finally, activation of fibrinolysis leads to breakdown of fibrin monomers, formation of fibrin thrombi, and increased levels of circulating fibrinogen. In most patients with DIC, the fibrinolytic response is brisk, which explains why most patients with DIC present with bleeding and prolonged clotting times.

## PATTERNS OF DIC

The clinical manifestations of DIC in a given patient depend on the balance of throbin activation and secondary fibrinolysis as well as the patient's ability to compensate for the DIC. Patients with DIC present in 1 of 4 patterns: they can be asymptomatic, presenting with laboratory evidence of DIC but no bleeding or thrombosis, or present with overt bleeding, thrombosis, or purpura fulminans.[1,3] Asymptomatic presentation is often seen in patients with sepsis or cancer. However, these patients can rapidly become symptomatic with progression of the underlying disease. Bleeding in DIC results from a combination of factor depletion, platelet dysfunction, thrombocytopenia, and excessive fibrinolysis.[1] These patients may present with diffuse bleeding from multiple sites (eg, intravenous sites, areas of instrumentation). Despite the general activation of the coagulation process, thrombosis is unusual in most patients with acute DIC. The exceptions include patients with cancer, trauma patients, and certain obstetrical patients. Most often the thrombosis is venous, but arterial thrombosis and nonbacterial thrombotic endocarditis have been reported.[6] Purpura fulminans, a severe form of DIC, is discussed in detail in the Specific DIC Syndromes section.

## DIAGNOSIS

The diagnosis DIC is not based solely on laboratory testing but rather requires interpreting the appropriate tests in the context of the patient's presentation and underlying condition (**Table 2**). Repeat testing is necessary given the dynamic nature of DIC. Screening tests for DIC include the

**Table 2.** Testing for Disseminated Intravascular Coagulation

| | |
|---|---|
| Prothrombin time-international normalized ratio, activated partial thromboplastin time, fibrinogen level | Nonspecific |
| Protamine sulfate test: detects circulating fibrin monomers | Specific but not sensitive |
| Ethanol gel test: detects circulating fibrin monomers | Sensitive but not specific |
| Fibrin(ogen) degradation products | |
| D-dimer test (fibrin degradation product) | |

prothrombin time (PT) activated partial thromboplastin time (aPTT), platelet count, and fibrinogen level. The PT-INR and aPPT are usually elevated in severe DIC but may be normal or shortened in chronic forms.[7] One may also see a shortened aPTT in severe acute DIC due to large amounts of activated II and factor X "bypassing" the contact pathway. APTTs as short as 10 seconds have been seen in acute DIC. The platelet count is usually reduced but may be normal in chronic DIC. Serum fibrinogen and platelets are decreased in acute DIC but also may be in the "normal" range in chronic DIC.[8] The most sensitive of the screening tests for DIC is a fall in the platelet count, with low counts seen in 98% of patients and counts under 50,000 cells/μL in 50%.[7,9] The least specific test is fibrinogen, which tends to fall below normal only in severe acute DIC.[7]

"Specific tests" for DIC allow one to deduce that abnormally high concentrations of thrombin are present. These include the ethanol gel and protamine sulfate tests, measurement of fibrin degradation product (FDP), and D-dimer levels. The ethanol gel and protamine tests detect circulating fibrin monomers. Circulating fibrin monomers are seen when thrombin acts on fibrinogen. Usually the monomer polymerizes with the fibrin clot, but when there is excess thrombin these monomers continue to circulate. Detection of circulating fibrin monomer means there is too much IIa and therefore DIC is present.

FDPs are produced when plasmin acts on the fibrin/fibrinogen molecule to cleave the molecule in specific places. FDP levels are elevated in the setting of increased fibrin/fibrinogen destruction, as occurs with DIC and fibrinolysis. FDP levels are typically mildly elevated in renal and liver disease due to reduced clearance.

When fibrin monomers bind to form a thrombus, factor XIII acts to bind the monomers together to form a dense network of fibrin polymer. One of the bonds created binds the fibrin "D" domains together, creating a bond that is resistant to plasmin. When the thrombus is lysed, this dimer remains and this degradation fragment is known as the D-dimer. High levels of D-dimer indicate that IIa has acted on fibrinogen to form a fibrin monomer that bonded to another fibrin monomer and that this thrombus was lysed by plasmin. Because an elevated D-dimer level can occur due to other causes (eg, exercise, surgery), an elevated D-dimer must be interpreted in the context of the clinical situation.[9]

Several other tests are sometimes helpful in diagnosing DIC. The thrombin time test is performed by adding thrombin to plasma. Thrombin times are increased in DIC (FDPs interfere with polymerization) and dysfibrinogenemia and in the presence of low fibrinogen levels and the presence of heparin (very sensitive). Reptilase time is the same as thrombin time but is performed with a snake venom that is insensitive to heparin. Reptilase time is elevated in the same conditions as the thrombin time, with the exception of the presence of heparin. Thrombin time and reptilase time are most useful in evaluation of dysfibrinogenemia. $F_{1.2}$ is a small peptide cleaved off when prothrombin is activated to thrombin. Thus, high

levels of $F_{1.2}$ are found in DIC but can be seen in other thrombotic disorders. This test's clinical value remains limited.

A scoring system to both diagnose and quantify DIC has been proposed (**Figure**).[9,10] This system is especially helpful for clinical trials. One difficulty of using this system in clinical settings is that it requires the measurement of PT, which has not been standardized and often is not reported by clinical laboratories.

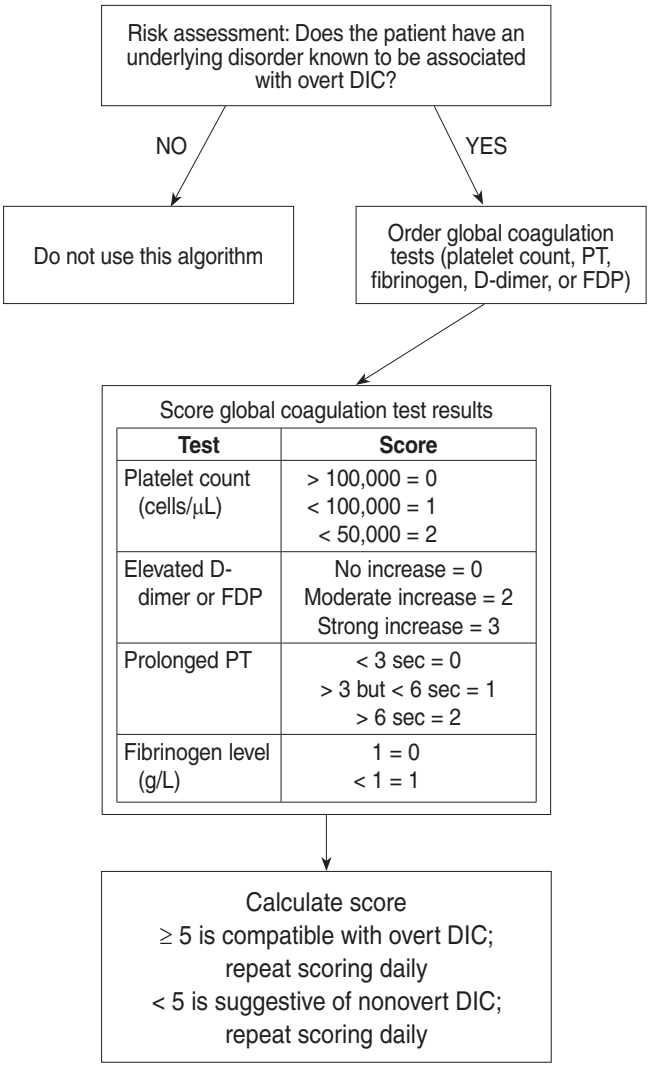



**Figure.** Disseminated intravascular coagulation (DIC) scoring system. FDP = fibrin degradation product; PT = prothrombin time. (Adapted from Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol 2009;145:24–33; *and* Levi M. Disseminated intravascular coagulation. Crit Care Med 2007;35:2191–5.)

## MIMICS OF DIC

It is important to recognize coagulation syndromes that resemble DIC, especially those with specific therapies that differ from those used to treat DIC. The syndromes most frequently encountered are thrombotic thrombocytopenic purpura (TTP) and catastrophic antiphospholipid antibody syndrome (APS). An important clue to recognizing both these syndromes is that, unlike DIC, there is no primary disorder (eg, cancer, sepsis) that is driving the coagulation abnormalities.

TTP should be suspected when a patient presents with any combination of thrombocytopenia, microangiopathic hemolytic anemia (schistocytes and signs of hemolysis), and end-organ damage.[11–13] Patients with TTP most often present with intractable seizures, strokes, or sequela of renal insufficiency. Many patients who present with TTP have been misdiagnosed as having sepsis, "lupus flare," or vasculitis. The key diagnostic differentiator between TTP and DIC is the lack of activation of coagulation with TTP—fibrinogen is normal and D-dimers are minimally or not elevated. In TTP the lactate dehydrogenase level is invariably elevated, often 2 to 3 times normal.[14] The importance of identifying TTP is that untreated TTP is rapidly fatal. Mortality in the pre–plasma exchange era ranged from 95% to 100%. Today plasma exchange therapy is the foundation of TTP treatment and has reduced mortality to less than 20%.[12,15–17]

Rarely patients with APS can present with fulminant multiorgan system failure.[18–21] Catastrophic

**Table 3.** Transfusion Therapy of DIC: Management Guidelines

| Test Result | Therapy |
|---|---|
| Platelets < 50,000–75,000 cells/μL | Platelet concentrates or 6–8 packs of single donor platelets |
| Fibrinogen < 125 mg/dL | 10 units of cryoprecipitate |
| Hematocrit < 30% | Packed red cells |
| PT/INR > 2.0 and aPTT abnormal | 2 to 4 units of FFP |

aPTT = activated partial thromboplastin time; FFP = fresh frozen plasma; INR = international normalized ratio; PT = prothrombin time.

APS is caused by widespread microthrombi in multiple vascular fields. These patients develop renal failure, encephalopathy, adult respiratory distress syndrome (often with pulmonary hemorrhage), cardiac failure, dramatic livido reticularis, and worsening thrombocytopenia. Many of these patients have preexisting autoimmune disorders and high-titer anticardiolipin antibodies. It appears that the best therapy for these patients is aggressive immunosuppression with plasmapheresis, followed by intravenous cyclophosphamide monthly.[21] Early recognition of this syndrome can lead to quick therapy and resolution of the multiorgan system failure.

## TREATMENT

The main focus of treating DIC is addressing the underlying cause that is driving the thrombin generation.[1,2,4,22,23] Fully addressing the underlying cause may not be possible or may take time, and in the meantime it is necessary to disrupt the cycle of thrombosis and/or hemorrhage. In the past, there was concern about using factor replacement due to fears of "feeding the fire," or perpetuating the cycle of thrombosis. However, these concerns are not supported by evidence, and one must replace factors if depletion occurs and bleeding ensues.[24]

Transfusion therapy of the patient with DIC is guided by the 5 laboratory tests that reflect the basic parameters essential for both hemostasis and blood volume status:[25,26] hematocrit, platelet count, PT-INR, aPTT, and fibrinogen level. Replacement therapy is based on the results of these laboratory tests and the patient's clinical situation (**Table 3**). The transfusion threshold for a low hematocrit depends on the stability of the patient. If the hematocrit is below 30% and the patient is bleeding or hemodynamically unstable, one should transfuse packed red cells. Stable patients can tolerate lower hematocrits and an aggressive transfusion policy may be detrimental.[27,28] Due to both the bleeding and platelet dysfunction in DIC, maintaining a platelet count of more than 50,000 cells/μL is reasonable.[25,29] The dose of platelets to be transfused is 6 to 8 platelet concentrates or 1 plateletpheresis unit. In patients with a fibrinogen level less than 100 mg/dL, transfusion of 10 units of cryoprecipitate is expected to increase the plasma fibrinogen level by 100 mg/dL. In patients with an INR greater than 2 and an abnormal aPTT, one can give 2 to 4 units of fresh frozen plasma (FFP).[23] For an aPTT greater than 1.5 times normal, 4 units of plasma should be given. Elevation of the aPTT above 1.8 times normal is associated with bleeding in trauma patients.[30] Patients with marked abnormalities, such as an aPTT increased 2 times normal, may require aggressive therapy with at least 15 to 30 mL/kg (4–8 units for an average adult) of plasma.[31]

The basic 5 laboratory tests should be repeated after administering the blood products to ensure that adequate replacement therapy was given for the coagulation defects. Frequent checks of the coagulation tests also allow rapid identification and therapy of new coagulation defects in a timely fashion. A flow chart of the test and the blood products administered should also be maintained. This documentation is important in acute situations such as trauma or obstetrical bleeding.

In theory since DIC is the manifestation of exuberant thrombin production, blocking thrombin with heparin should decrease or shut down DIC. However, studies have shown that administration of heparin in most patients leads to excessive bleeding. Currently, heparin therapy is reserved for the patient who has thrombosis as a component of their DIC.[2,24,32] Given the coagulopathy that is often present, one should use specific heparin levels instead of the aPTT to monitor anticoagulation.[33,34]

## SPECIFIC DIC SYNDROMES

### SEPSIS/INFECTIOUS DISEASE

Classically, it was believed that gram-negative bacteria can lead to the development of DIC by causing tissue factor exposure via their production of endotoxin, but recent studies indicate that DIC can be seen with any overwhelming infection.[35] There are several potential avenues by which infections can lead to DIC.[36] As mentioned, gram-negative bacteria produce endotoxin that can directly lead to tissue factor exposure with resulting excess thrombin generation. In addition, any infection can lead to expression of inflammatory cytokines that induce tissue factor expression by endothelium and monocytes. Some viruses and rickettsia can directly infect the vascular endothelium, converting it from an antithrombotic to a prothrombotic phenotype. The hypotension produced by sepsis leads to tissue hypoxia, which results in more DIC. The coagulopathy can range from subtle abnormalities of testing to purpura fulminans. Thrombocytopenia is worsened by cytokine-induced hemophagocytic syndrome

As with all forms of DIC, empiric therapy directed at the most likely source of infection and maintaining hemodynamic stability are key to therapy. As discussed below, heparin and other forms of coagulation replacement therapy, with the controversial exception of recombinant human activated protein C (rhAPC), or drotrecogin alfa (activated), are of no benefit.

### PURPURA FULMINANS

DIC in association with necrosis of the skin is seen in 2 situations, primary and secondary purpura fulminans.[37,38] Primary purpura fulminans is most often seen after a viral infection.[39] In these patients, the purpura fulminans starts with a painful red area on an extremity that rapidly progresses to a black ischemic area. Acquired deficiency of protein S is found in many patients.[37,40,41] Secondary purpura fulminans is most often associated with meningococcemia infections but can be seen in any patient with overwhelming infection.[42–44] Postsplenectomy sepsis syndrome patients and those with functional hyposplenism due to chronic liver diseases are also at risk.[45] Patients present with signs of sepsis, and the skin lesions often involve the extremities and may lead to amputations. As opposed to primary purpura fulminans, those with the secondary form will have symmetrical distal ischemia (toes and fingers) that ascends as the process progresses. Rarely, adrenal infarction (Waterhouse-Friderichsen syndrome) can occur, which leads to severe hypotension.[35]

Therapy for purpura fulminans is controversial. Primary purpura fulminans, especially in those with post-varicella autoimmune protein S deficiency, has responded to plasma infusion titrated to keep the protein S level above 25%.[37] Intravenous immunoglobulin has also been reported to help decrease the anti-protein S antibodies. Heparin has been reported to control the DIC and extent of necrosis.[46] The starting dose in these patients is 5 to 8 units/kg/hr.[2]

**Table 4.** Treatment of Purpura Fulminans with Recombinant Human Activated Protein C (rhAPC)

| |
|---|
| Administer rhAPC 24 μg/kg/hr for 96 hours |
| Initiate blood product support to maintain: |
| An INR < 2 |
| aPTT less than 1.8 times normal (rhAPC will raise aPTT by 5–7 sec) |
| Platelet count over 50,000 cells/μL |
| Consider continuous veno-venohemofiltration |

aPTT = activated partial thromboplastin time; INR = international normalized ratio.

Patients with secondary purpura fulminans have been treated with plasma drips, plasmapheresis, and continuous plasma ultrafiltration.[46–49] Heparin therapy alone has not been shown to improve survival.[50] Much attention has been given to replacement of natural anticoagulants such as protein C and antithrombin as therapy for purpura fulminans, but unfortunately randomized trials using antithrombin have shown mostly negative results.[37,41,51–53] Trials using either zymogen protein C concentrates or rhAPC have shown more promise in controlling the coagulopathy of purpura fulminans and improving outcomes in sepsis.[47,54–57] Although bleeding is a concern with use of protein C, most complications occur in patients with platelet counts under 30,000 cells/μL or in those who have meningitis.[58] If rhAPC is used, one should also very carefully monitor other parameters of coagulation (**Table 4**). Many patients will need debridement and amputation for their necrotic limbs, with one review showing that approximately 66% of patients require amputations.[38]

## TRAUMA

Currently, the most common cause of acute DIC is trauma. The coagulation defects that occur in trauma patients are complex in origin.[59] The most common etiologies are dilution of hemostatic factors by fluid or blood resuscitation, hypothermia, tissue damage from trauma, and effects of underlying diseases. Trauma patients are prone to hypothermia, and this can be the major complicating factor in their bleeding.[60,61] Patients may be out "in the field" for a prolonged period of time and be hypothermic on arrival.[62] Packed red cells are stored at 4°C, and the infusion of 1 unit can lower the body temperature by 0.16°C.[63] Hypothermia has profound effects on the coagulation system that are associated with clinical bleeding.[60,64,65] Even modest hypothermia can greatly augment bleeding and needs to be treated or prevented.

The initial management of the bleeding trauma patient consists of obtaining the basic set of coagulation tests.[59,66,67] If the patient is having obvious massive hemorrhage, red cells and plasma should be empirically infused until the results of laboratory tests are received. Since patients with head trauma can develop defibrination, therapy with cryoprecipitate and plasma should be considered.[68] Hypothermia can be prevented by several measures. One is to transfuse the blood through blood warmers. Devices are available that can warm a unit of blood per minute. An increasingly used technique is to perform "damage control" surgery. Patients are initially stabilized with control of damaged vessels and packing of oozing sites.[69] Then the patient is taken to the intensive care unit to be warmed and have coagulation defects corrected.

## PREGNANCY-RELATED DIC SYNDROMES

### Acute DIC of Pregnancy

Pregnancy can be associated with the rapid onset of severe DIC in 2 situations, abruption and amniotic fluid embolism.[70,71] The separation of the placenta from the uterine wall creates a space for blood to occupy. Because the placenta is rich in tissue factor, this separation leads to activa-

tion of coagulation both locally and systemically. Release of blood when this space reaches the vaginal opening can lead to rapid hemorrhage, further augmenting the coagulation abnormalities. Fetal demise due to placental insufficiency can also worsen the DIC. Management depends on the size of the abruption and the clinical status of both mother and fetus.[70] For severe bleeding and DIC, blood product support is crucial to allow safe delivery. For smaller abruption, close observation with early delivery is indicated.

Amniotic fluid embolism occurs suddenly with the vascular collapse of the woman soon after delivery. Due to the presence of procoagulant rich fluid in the circulatory system, there is often overwhelming DIC. Therapy is directed at both supporting blood volume and correcting hemostatic defects.

### HELLP Syndrome

The HELLP (**h**emolysis, **e**levated **l**iver tests, **l**ow **p**latelets) syndrome is a variant of preeclampsia.[72] Classically, HELLP syndrome occurs after 28 weeks of gestation in a patent suffering from preeclampsia, but can occur as early as 22 weeks in patients with APS.[73–75] The preeclampsia need not be severe. The first sign of HELLP is a decrease in the platelet count followed by abnormal liver function tests. Signs of hemolysis are present with abundant schistocytes on the smear and a high lactate dehydrogenase level. HELLP can progress to liver failure, and deaths due to hepatic rupture have also been reported. Unlike TTP, fetal involvement is present in the HELLP syndrome, with fetal thrombocytopenia reported in 30% of cases. In severe cases, elevated D-dimers consistent with DIC are also found. Delivery of the child will most often result in cessation of the HELLP syndrome, but refractory cases require treatment with dexamethasone and plasma exchange.[76] Patients should be closely observed for 1 to 2 days after delivery as the hematologic picture can transiently worsen before improving.[77]

### Acute Fatty Liver of Pregnancy

Fatty liver of pregnancy also occurs late in pregnancy and is associated with preeclampsia in 50% of cases.[78,79] Patients first present with nonspecific symptoms of nausea and vomiting but can progress to fulminant liver failure. Patients develop thrombocytopenia early in the course, but in the later stages can develop DIC and very low fibrinogen levels. Mortality rates without therapy can be as high as 90%. Low blood glucose and high ammonia levels can help distinguish fatty liver from other pregnancy complications.[80] Treatment consists of prompt delivery of the child and aggressive blood product support.

### Retained Dead Fetus Syndrome

This syndrome is becoming increasingly rare in modern practices. The presence of a dead fetus for many weeks (usually $\geq 5$) can result in a chronic DIC state with fibrinogen depletion and coagulopathy. In some women, these abnormalities worsen at delivery. In a stable patient, a short trial of heparin prior to planning delivery can control the DIC to allow the coagulopathy to stabilize.

## DRUG-INDUCED HEMOLYTIC-DIC SYNDROMES

A severe variant of the drug-induced immune complex hemolysis associated with DIC has been recognized. Although rare, this syndrome has been reported in patients who receive certain second- and third-generation cephalosporins (especially cefotetan and ceftriaxone).[81–86] The clinical syndrome starts 7 to 10 days after the drug is administered, and often the patient has

received the antibiotic only for surgical prophylaxis. The patient develops severe Coombs' positive hemolysis with hypotension and DIC. The patients are often believed to have sepsis and often re-exposed to the cephalosporin, resulting in worsening of the clinical picture. The outcome is often fatal due to massive hemolysis and thrombosis.[83,87–89]

Quinine is associated with a unique syndrome of drug-induced DIC.[90–93] Approximately 24 to 96 hours after quinine exposure, the patient becomes acutely ill with nausea and vomiting. The patient then develops a microangiopathic hemolytic anemia, DIC, and renal failure. Besides having antiplatelet antibodies, some patients also have antibodies binding to red cells and neutrophils, which may lead to the more severe syndrome. Despite therapy, patients with quinine-induced TTP have a high incidence of chronic renal failure.

Treatment of the drug-induced hemolytic-DIC syndrome is anecdotal. Patients have responded to aggressive therapy, including plasma exchange, dialysis, and prednisone.[91] Early recognition of the hemolytic anemia and suspicion that it is drug related is important for early diagnosis so that the drug can be discontinued.

## CANCER

Cancers, primarily adenocarcinomas, can result in DIC. The classic Trousseau's syndrome referred to the association of migratory superficial thrombophlebitis with cancer[94] but now refers to cancer associated with thrombotic DIC.[95,96] Highly vascular tumor cells are known to express tissue factor,[96,97] and some tumor cells can express a direct activator of factor X ("cancer procoagulant"). Unlike many DIC states, DIC caused by cancer presents with thrombosis instead of bleeding. This may be due to the inflammatory state which accompanies cancer, or it may be a part of the chronic nature of cancer DIC biology that allows time for the body to compensate for loss of coagulation factors. In some patients, thrombosis is the first sign of an underlying cancer, sometimes predating the cancer diagnosis by months.[97] Rarely the DIC can result in nonthrombotic endocarditis with microemboli leading to widespread small-vessel thrombosis.[95]

Since there is no effective antineoplastic therapy for many tumors associated with Trousseau's syndrome, DIC therapy is aimed at suppressing thrombosis. An exception is prostate cancer, where hormonal therapy can markedly decrease the DIC.[98] Because the tumor directly activates coagulation factors, inhibition of active enzymes via heparin has been shown to result is lower rates of recurrence than use of warfarin.[96,97] Clinical trials have demonstrated that heparin therapy is associated with a lower thrombosis recurrence rate than warfarin.[99] In some patients, the thrombotic process is so vigorous that new thrombosis can be seen within hours of stopping heparin.[94]

## ACUTE PROMYELOCYTIC LEUKEMIA

The hemostatic defects in patients with acute promyelocytic leukemia (APL) are multiple.[100] Most, if not all, patients with APL have evidence of DIC at the time of diagnosis. Patients with APL have a higher risk of death during induction therapy as compared with patients with other forms of leukemia, with death most often due to bleeding. Once in remission, APL patients have a higher cure rate than most patients with leukemia. APL is also unique among leukemias in that biological therapy with retinoic acid or arsenic is effective in inducing remission and cure in most patients.

APL patients can present with pancytopenia due to leukemic marrow replacement or with diffuse bleeding due to DIC and thrombocytopenia. Life-threatening bleeding such as intracranial hemorrhage may occur at any time until the leukemia is put into remission. The etiology of the hemostatic defects in APL is complex and is thought to be the result of DIC, fibrinolysis, and the release of other procoagulant enzymes.[100] The diagnosis of APL can be straightforward when the leukemic cells are promyelocytes with abundant Auer rods, although some patients have the microgranular form without obvious Auer rods. The precise diagnosis requires molecular methods. Upon diagnosis of APL, one should obtain a complete coagulation profile, including INR, aPTT, fibrinogen, platelet count, and D-dimers. Change in fibrinogen levels tends to be a good marker of progress in treating the coagulation defects.

Therapy of APL involves treating both the leukemia and the coagulopathy. Currently, the standard treatment for APL is trans-retinoic acid (ATRA) in combination with chemotherapy.[101,102] This approach will induce remission in over 90% of patients, and a sizable majority of these patients will be cured of their APL. ATRA therapy will also lead to early correction of the coagulation defects, often within the first week of therapy. This is in stark contrast to the chemotherapy era when the coagulation defects would become worse with therapy. Rare reports of massive thrombosis complicating therapy with ATRA exist, but the relationship to either the APL or ATRA is unknown.

Therapy for the coagulation defects consists of aggressive transfusion therapy support and possible use of other pharmacologic agents to control DIC.[102,103] One should try to maintain the fibrinogen level at over 100 mg/dL and the platelet count at over 50,000 cells/μL. Controversy still exists over the role of heparin in therapy of APL.[104] Although attractive for its ability to quench thrombin, heparin use can lead to profound bleeding and has fallen out of favor.

## SNAKEBITES

Snake envenomation can lead to direct activation of multiple coagulation enzymes, including factors V, X, thrombin, and protein C as well as lead to cleavage of fibrinogen.[105] Envenomation can also activate coagulation and damage vascular endothelium. The DIC can be enhanced by widespread tissue necrosis and hypotension. The key to management of snake bites is administration of specific antivenom. The role of factor replacement is controversial but indicated if there is clinical bleeding. One confounder is that some snake venoms, especially rattlesnake, can induce reversible platelet aggregation that corrects with antivenom.

## LOCAL VASCULAR ABNORMALITIES

Abnormal vascular structures, including vascular tumors, vascular malformations, and aneurysms, can lead to localized areas of thrombin generation that can "spill-over" into the general circulation, leading to DIC. The diagnosis Kasabach-Merritt phenomenon should be reserved for children with vascular tumors such as angioma or hemangioendothelioma.[106] Therapy depends on the lesion. Embolization to reduce blood flow of vascular malformations can either be definitive or stabilize the patient for surgery. Aneurysms can be repaired by surgery or stenting. Rare patients with aneurysms with significant coagulopathy may require heparin to increase the fibrinogen level before surgery. Kasabach-Merritt disease can respond to steroids or therapy with vincristine or interferon.[106]

## SUMMARY

At the most basic level, DIC is the excess activity of thrombin. However, the clinical presentation and therapy can differ greatly depending on the primary cause. Both diagnosis and therapy involve close coordination of laboratory data and clinical assessment.

### BOARD REVIEW QUESTIONS

**Test your knowledge of this topic. Go to www.turner-white.com and select Hematology from the drop-down menu of specialties.**

## REFERENCES


1. Carey MJ, Rodgers GM. Disseminated intravascular coagulation: clinical and laboratory aspects. Am J Hematol 1998;59:65–73.
2. De Jonge E, Levi M, Stoutenbeek CP, Van Deventer SJH. Current drug treatment strategies for disseminated intravascular coagulation. Drugs 1998;55:767–77.
3. Baker WF, Jr. Clinical aspects of disseminated intravascular coagulation: a clinician's point of view. Sem Thrombosis Hemostasis 1989;15:1–57.
4. Levi M, ten Cate H. Disseminated intravascular coagulation. N Engl J Med 1999;341:586–92.
5. Faust SN, Levin M, Harrison OB, et al. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. N Engl J Med 2001;345:408–16.
6. Sharma S, Mayberry JC, DeLoughery TG, Mullins RJ. Fatal cerebroembolism from nonbacterial thrombotic endocarditis in a trauma patient: case report and review. Military Medicine 2000;165:83–5.
7. Yu M, Nardella A, Pechet L. Screening tests of disseminated intravascular coagulation: guidelines for rapid and specific laboratory diagnosis. Crit Care Med 2000;28: 1777–80.
8. Mant MJ, King EG. Severe, acute disseminated intravascular coagulation. A reappraisal of its pathophysiology, clinical significance, and therapy based on 47 patients. Am J Med 1979;67:557–63.
9. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol 2009;145:24–33.
10. Levi M. Disseminated intravascular coagulation. Crit Care Med 2007;35:2191–5.
11. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med 2006;354:1927–35.
12. George JN. How I treat patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Blood 2000;96:1223–9.
13. Murrin RJ, Murray JA. Thrombotic thrombocytopenic purpura: aetiology, pathophysiology and treatment. Blood Rev 2006;20:51–60.
14. Patton JF, Manning KR, Case D, Owen J. Serum lactate dehydrogenase and platelet count predict survival in thrombotic thrombocytopenic purpura. Am J Hematol 1994;47:94–9.
15. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. N Engl J Med 1991;325:393–7.
16. Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome—clinical experience in 108 patients. N Engl J Med 1991;325:398–403.
17. Kaplan BS, Trachtman H. Improve survival with plasma exchange thrombotic thrombopenic purpura-hemolytic uremic syndrome. Am J Med 2001;110:156–7.
18. Asherson RA. The catastrophic antiphospholipid syndrome [editorial]. J Rheumatol 1992;19:508–12.
19. Asherson RA, Piette JC. The catastrophic antiphospholipid syndrome 1996: acute multi-organ failure associated with antiphospholipid antibodies: a review of 31 patients. Lupus 1996;5:414–7.
20. Asherson RA, Cervera R. Castastrophic antiphospholipid syndrome. Curr Opinion Hematol 2000;5:325–9.
21. Merrill JT, Asherson RA. Catastrophic antiphospholipid syndrome. Nat Clin Pract Rhuem 2006;2:81–9.
22. Hoffman JN, Faist E. Coagulation inhibitor replacement during sepsis: useless? Crit Care Med 2000;28(9 Suppl): S74–6.
23. Wada H, Asakura H, Okamoto K, et al. Expert consensus for the treatment of disseminated intravascular coagulation in Japan. Japanese Society of Thrombosis Hemostasis/DIC subcommittee. Thromb Res 2009 Sep 24. [Epub ahead of print].
24. Feinstein DI. Diagnosis and management of disseminated intravascular coagulation: the role of heparin therapy. Blood 1982;60:284–7.
25. Counts RB, Haisch C, Simon TL, et al. Hemostasis in massively transfused trauma patients. Ann Surg 1979;190: 91–9.
26. Stainsby D, MacLennan S, Hamilton PJ. Management of massive blood loss: a template guideline. Br J Anaesth

2000;85:487–91.
27. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409–17.
28. Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal haemorrhage. Br J Surg 1986;73:783–5.
29. Miller RD, Robbins TO, Tong MJ, Barton SL. Coagulation defects associated with massive blood transfusions. Ann Surg 1971;174:794–801.
30. Ciavarella D, Reed RL, Counts RB, et al. Clotting factor levels and the risk of diffuse microvascular bleeding in the massively transfused patient. Br J Haematol 1987;67:365–8.
31. Chowdhury P, Saayman AG, Paulus U, et al. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. Br J Haematol 2004;125:69–73.
32. Callander N, Rapaport SI. Trousseau's syndrome. West J Med 1993;158:364–71.
33. Brill-Edwards P, Ginsberg JS, Johnston M, Hirsh J. Establishing a therapeutic range for heparin therapy. Ann Intern Med 1993;119:104–9.
34. Olson JD, Arkin CF, Brandt JT, et al. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin therapy. Arch Pathol Lab Med 1998;122:782–8.
35. Yoshikawa T, Tanaka KR, Guze LB. Infection and disseminated intravascular coagulation. Medicine (Baltimore) 1971;50:237–58.
36. Jagneaux T, Taylor DE, Kantrow SP. Coagulation in sepsis. Am J Med Sci 2004;328:196–204.
37. Darmstadt GL. Acute infectious purpura fulminans: pathogenesis and medical management. Pediatr Dermatol 1998; 15:169–83.
38. Davis MD, Dy KM, Nelson S. Presentation and outcome of purpura fulminans associated with peripheral gangrene in 12 patients at Mayo Clinic. J Am Acad Dermatol 2007;57:944–56.
39. Spicer TE, Rau JM. Purpura fulminans. Am J Med 1976; 61:566–71.
40. Josephson C, Nuss R, Jacobson L, et al. The varicella-autoantibody syndrome. Pediatr Res 2001;50:345–52.
41. Smith OP, White B. Infectious purpura fulminans: diagnosis and treatment. Br J Haematol 1999;104:202–7.
42. Gamper G, Oschatz E, Herkner H, et al. Sepsis-associated purpura fulminans in adults. Wien Klin Wochenschr 2001;113(3-4):107–12.
43. Ward KM, Celebi JT, Gmyrek R, Grossman ME. Acute infectious purpura fulminans associated with asplenism or hyposplenism. J Am Acad Dermatol 2002;47:493–6.
44. Childers BJ, Cobanov B. Acute infectious purpura fulminans: a 15-year retrospective review of 28 consecutive cases. Am Surg 2003;69:86–90.
45. Carpenter CT, Kaiser AB. Purpura fulminans in pneumococcal sepsis: case report and review. Scand J Infect Dis 1997;29:479–83.
46. Duncan A. New therapies for severe meningococcal disease but better outcomes? Lancet 1997;350:1565–6.
47. Smith OP, White B, Vaughan D, et al. Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura fulminans. Lancet 1997;350:1590–3.
48. Branson HE, Katz J. A structured approach to the management of purpura fulminans. J Natl Med Assoc 1983;75:821–5.
49. Nolan J, Sinclair R. Review of management of purpura fulminans and two case reports. Br J Anaesth 2001;86: 581–6.
50. Manios SG, Kanakoudi F, Maniati E. Fulminant meningococcemia. Heparin therapy and survival rate. Scand J Infect Dis 1971;3:127–33.
51. Giudici D, Baudo F, Palareti G, et al. Antithrombin replacement in patients with sepsis and septic shock. Haematologica 1999;84:452–60.
52. Fourrier F, Jourdain M, Tournoys A. Clinical trial results with antithrombin III in sepsis. Crit Care Med 2000;28 (9 Suppl):S38–43.
53. Levi M, De Jonge E, van der PT, ten Cate H. Novel approaches to the management of disseminated intravascular coagulation. Crit Care Med 2000;28(9 Suppl):S20–4.
54. Rivard GE, David M, Farrell C, Schwarz HP. Treatment of purpura fulminans in meningococcemia with protein C concentrate. J Pediatr 1995;126:646–52.
55. White B, Livingstone W, Murphy C, et al. An open-label study of the role of adjuvant hemostatic support with protein C replacement therapy in purpura fulminans-associated meningococcemia. Blood 2000;96:3719–24.
56. Aoki N, Matsuda T, Saito H, et al. A comparative double-blind randomized trial of activated protein C and unfractionated heparin in the treatment of disseminated intravascular coagulation. Int J Hematol 2002;75:540–7.
57. Schellongowski P, Bauer E, Holzinger U, et al. Treatment of adult patients with sepsis-induced coagulopathy and purpura fulminans using a plasma-derived protein C concentrate (Ceprotin). Vox Sang 2006;90:294–301.
58. Taylor FB, Kinasewitz G. Activated protein C in sepsis. J Thromb Haemost 2004;2:708–17.
59. DeLoughery TG. Coagulation defects in trauma patients: etiology, recognition, and therapy. Crit Care Clin 2004; 20:13–24.
60. Eddy VA, Morris JA Jr, Cullinane DC. Hypothermia, coagulopathy, and acidosis. Surg Clin North Am 2000;80:

845–54.
61. Peng RY, Bongard FS. Hypothermia in trauma patients. J Am Coll Surg 1999;188:685–96.
62. Steinemann S, Shackford SR, Davis JW. Implications of admission hypothermia in trauma patients. J Trauma 1990;30:200–2.
63. Rajek A, Greif R, Sessler DI, et al. Core cooling by central venous infusion of ice-cold (4 degrees C and 20 degrees C) fluid: isolation of core and peripheral thermal compartments. Anesthesiol 2000;93:629–37.
64. Watts DD, Trask A, Soeken K, et al. Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. J Trauma 1998;44:846–54.
65. Ferrara A, MacArthur JD, Wright HK, et al. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. Am J Surg 1990;160:515–8.
66. Robb WJ. Massive transfusion in trauma. AACN Clinical Issues 1999;10:69–84.
67. Lynn M, Jeroukhimov I, Klein Y, Martinowitz U. Updates in the management of severe coagulopathy in trauma patients. Intensive Care Med 2002;28:Suppl 2:S241–7.
68. Goodnight SH, Kenoyer G, Rapaport SI, et al. Defibrination after brain-tissue destruction: a serious complication of head injury. N Engl J Med 1974;290:1043–7.
69. Stone HH, Strom PR, Mullins RJ. Management of the major coagulopathy with onset during laparotomy. Ann Surg 1983;197:532–5.
70. Hall DR. Abruptio placentae and disseminated intravascular coagulopathy. Semin Perinatol 2009;33:189–95.
71. Thachil J, Toh CH. Disseminated intravascular coagulation in obstetric disorders and its acute haematological management. Blood Rev 2009;23:167–76.
72. Baxter JK, Weinstein L. HELLP syndrome: the state of the art. Obstet Gynecol Surv 2004;59:838–45.
73. Egerman RS, Sibai BM. HELLP syndrome. Clin Obstetr Gynecol 1999;42:381–9.
74. Saphier CJ, Repke JT. Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: a review of diagnosis and management. Sem Perinatol 1998;22:118–33.
75. Le Thi TD, Tieulie N, Costedoat N, et al. The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. Ann Rheum Dis 2005; 64:273–8.
76. Martin JN Jr, Perry KG Jr, Blake PG, et al. Better maternal outcomes are achieved with dexamethasone therapy for postpartum HELLP (hemolysis, elevated liver enzymes, and thrombocytopenia) syndrome. Am J Obstet Gynecol 1997;177:1011–7.
77. Magann EF, Martin JN Jr. Twelve steps to optimal management of HELLP syndrome. Clinical Obstet Gynecol 1999;42:532–50.
78. Jwayyed SM, Blanda M, Kubina M. Acute fatty liver of pregnancy. J Emerg Medi 1999;17:673–7.
79. Bacq Y. Acute fatty liver of pregnancy. Sem Perinatol 1998;22:134–40.
80. Egerman RS, Sibai BM. Imitators of preeclampsia and eclampsia. Clin Obstet Gynecol 1999;42:551–62.
81. Garratty G. Immune cytopenia associated with antibiotics. Transfusion Medi Rev 1993;7:255–67.
82. Chenoweth CE, Judd WJ, Steiner EA, Kauffman CA. Cefotetan-induced immune hemolytic anemia. Clin Infect Dis 1992;15:863–5.
83. Garratty G, Nance S, Lloyd M, Domen R. Fatal immune hemolytic anemia due to cefotetan. Transfusion 1992; 32:269–71.
84. Endoh T, Yagihashi A, Sasaki M, Watanabe N. Ceftizoxime-induced hemolysis due to immune complexes: case report and determination of the epitope responsible for immune complex-mediated hemolysis. Transfusion 1999;39:306–9.
85. Arndt PA, Leger RM, Garratty G. Serology of antibodies to second- and third-generation cephalosporins associated with immune hemolytic anemia and/or positive direct antiglobulin tests. Transfusion 1999;39:1239–46.
86. Martin ME, Laber DA. Cefotetan-induced hemolytic anemia after perioperative prophylaxis. Am J Hematol 2006;81:186–8.
87. Bernini JC, Mustafa MM, Sutor LJ, Buchanan GR. Fatal hemolysis induced by ceftriaxone in a child with sickle cell anemia. J Pediatr 1995;126:813–5.
88. Borgna-Pignatti C, Bezzi TM, Reverberi R. Fatal ceftriaxone-induced hemolysis in a child with acquired immunodeficiency syndrome. Pediatr Infect Dis J 1995;14:1116–7.
89. Lascari AD, Amyot K. Fatal hemolysis caused by ceftriaxone. J Pediatr 1995;126:816–7.
90. Gottschall JL, Elliot W, Lianos E, et al. Quinine-induced immune thrombocytopenia associated with hemolytic uremic syndrome: a new clinical entity. Blood 1991;77:306–10.
91. Gottschall JL, Neahring B, McFarland JG, et al. Quinine-induced immune thrombocytopenia with hemolytic uremic syndrome: clinical and serological findings in nine patients and review of literature. Am J Hematol 1994;47:283–9.
92. Crum NF, Gable P. Quinine-induced hemolytic-uremic syndrome. South Med J 2000;93:726–8.
93. Vesely T, Vesely JN, George JN. Quinine-Induced thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS): frequency, clinical features, and long-term outcomes. Blood 2000;96:629 [abstract].
94. Bell WR, Starksen NF, Tong S, Porterfield JK. Trousseau's syndrome. Devastating coagulopathy in the absence of heparin. Am J Med 1985;79:423–30.
95. Sack GH, Levin J, Bell WR. Trousseau's syndrome and

other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinic, pathophysiologic, and therapeutic features. Medicine 1977;56:1–37.
96. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. Blood 2007;110:1723–9.
97. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. Lancet Oncol 2005;6:401–10.
98. de la Fouchardiere C, Flechon A, Droz JP. Coagulopathy in prostate cancer. Neth J Med 2003;61:347–54.
99. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest 2008;133(6 Suppl):454S–545S.
100. Arbuthnot C, Wilde JT. Haemostatic problems in acute promyelocytic leukaemia. Blood Rev 2006;20:289–97.
101. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood 2008;111:2505–15.
102. Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. Blood 2009;114:5126–35.
103. Falanga A, Rickles FR. Management of thrombohemorrhagic syndromes (THS) in hematologic malignancies. Hematology 2007;2007:165–71.
104. Sanz MA, Grimwade D, Tallman MS, et al. Guidelines on the management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 2009;113:1875–91.
105. Lu Q, Clemetson JM, Clemetson KJ. Snake venoms and hemostasis. J Thromb Haemost 2005;3:1791–9.
106. Rodriguez V, Lee A, Witman PM, Anderson PA. Kasabach-merritt phenomenon: case series and retrospective review of the mayo clinic experience. J Pediatr Hematol Oncol 2009;31:522–6.

*The distribution of this publication is made possible through the financial support of Merck*

The Hospital Physician® Board Review Manuals are published by Turner White Communications, Inc., an independent medical publisher dedicated to serving the information and education needs of clinical trainees and practicing physicians.

HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

**STATEMENT OF EDITORIAL PURPOSE**

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

**PUBLISHING STAFF**

**PRESIDENT, GROUP PUBLISHER**
Bruce M. White

**SENIOR EDITOR**
Robert Litchkofski

**EXECUTIVE VICE PRESIDENT**
Barbara T. White

**EXECUTIVE DIRECTOR OF OPERATIONS**
Jean M. Gaul

**PRODUCTION DIRECTOR**
Jeff White

**NOTE FROM THE PUBLISHER:**
This publication has been developed without involvement of or review by the American Board of Internal Medicine.

# Peripheral T-Cell Non-Hodgkin Lymphoma

**Series Editor and Contributor:**
**Eric D. Jacobsen, MD**

*Instructor of Medicine*
*Harvard Medical School;*
*Attending Physician*
*Dana-Farber Cancer Institute*
*Boston, MA*

## Table of Contents



**Cover Illustration by Kathryn K. Johnson**

# Peripheral T-Cell Non-Hodgkin Lymphoma

*Eric D. Jacobsen, MD*

## INTRODUCTION AND CLASSIFICATION

Peripheral T-cell lymphoma (PTCL) represents a heterogeneous collection of mature T- and NK-cell neoplasms. Most are clinically aggressive and all are uncommon. The descriptor "peripheral" does not refer to an anatomic location but rather the stage of development of the T cell. PTCLs derive from mature, post-thymic T cells as opposed to T-cell acute lymphoblastic leukemia/lymphoma, which derives from immature T cells.[1] The most recent World Health Organization (WHO) classification system for PTCL is shown in **Table 1**.[2] The histologies are categorized by clinical behavior, with the nodal, extranodal, and leukemic variants grouped together; however, these distinctions are not absolute, and there is substantial overlap in sites of involvement. This review will not focus on cutaneous T-cell lymphoma, which is clinically and biologically distinct from PTCL.

## EPIDEMIOLOGY

PTCL accounts for 5% to 10% of all cases of non-Hodgkin lymphoma (NHL) diagnosed in North America.[3] **Table 2** shows the relative frequency of various PTCL histologies.[4] In North America and Western Europe, the most common histologies are PTCL–not otherwise specified (NOS); anaplastic large cell lymphoma, T/null-cell type (ALCL); and angioimmunoblastic T-cell lymphoma (AILT). In parts of Asia, however, extranodal NK/T-cell lymphoma, nasal type (NK/TCL) and adult T-cell leukemia/lymphoma (ATLL) are quite prevalent.[5] The epidemiology of individual subtypes will be discussed in more detail in later sections.

## CLINICAL AND PATHOLOGIC FEATURES

The median age at diagnosis for most histologies is approximately 60 years, though histologies such as ALCL and hepatosplenic T-cell lymphoma affect adolescents and young adults.[6] There is a 1.5:1 male predominance.[3] Approximately 60% of patients present with stage IV disease. Fifty-six percent of patients will have nodal and extranodal involvement, while 30% have extranodal disease only.[4] Cutaneous involvement is far more common than with B-cell NHL.[7] The majority of patients will have an elevated serum lactate dehydrogenase (LDH), and a substantial

**Copyright 2010, Turner White Communications, Inc., Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications. The preparation and distribution of this publication are supported by sponsorship subject to written agreements that stipulate and ensure the editorial independence of Turner White Communications. Turner White Communications retains full control over the design and production of all published materials, including selection of topics and preparation of editorial content. The authors are solely responsible for substantive content. Statements expressed reflect the views of the authors and not necessarily the opinions or policies of Turner White Communications. Turner White Communications accepts no responsibility for statements made by authors and will not be liable for any errors of omission or inaccuracies. Information contained within this publication should not be used as a substitute for clinical judgment.**

**Table 1.** 2008 World Health Organization Classification of Mature T- and NK-Cell Neoplasms (Excluding Cutaneous T-cell Lymphoma)

| Nodal | Extranodal | Leukemic |
|---|---|---|
| Peripheral T-cell lymphoma, not otherwise specified | NK/T-cell lymphoma, nasal type | Adult T-cell leukemia/lymphoma |
| Anaplastic large cell lymphoma, ALK-positive | Enteropathy associated T-cell lymphoma | Aggressive NK-cell leukemia |
| Anaplastic large cell lymphoma, ALK-negative | Hepatosplenic T-cell lymphoma | T-cell prolymphocytic leukemia |
| Angioimmunoblastic T-cell lymphoma | Subcutaneous panniculitis-like T-cell lymphoma | T-cell large granular lymphocytic leukemia |

ALK = anaplastic lymphoma kinase.

percentage will have B symptoms of fever, night sweats, and/or weight loss. With some notable exceptions discussed later, there are few defined risk factors for PTCL.

Many types of PTCL can be confused clinically and pathologically with other types of lymphoma. For instance, PTCL can be confused with T-cell–rich diffuse large B-cell lymphoma, and often only extremely sensitive techniques such as T-cell receptor (TCR) gene rearrangement studies can distinguish the 2 entities.[8] PTCL can also be confused with lymphomatoid granulomatosis, which like PTCL often involves the skin and is Epstein-Barr virus (EBV)-positive.[9] ALCL commonly affects young patients, as do mediastinal diffuse large B-cell lymphoma and Hodgkin lymphoma, resulting in diagnostic confusion. Adding to the confusion, both Hodgkin lymphoma and ALCL can express CD30.[10] One study demonstrated that the concordance of PTCL diagnoses among expert pathologists using histologic criteria alone was extremely low, with concordance rates of 46% for ALCL and 41% for PTCL-NOS. A fairly high level of discordance remained even with the addition of immunohistochemistry: 85% for ALCL and 86% for PTCL-NOS.[4] Specific immunophenotypes for various PTCL histologies are discussed later in the article. In general, however, PTCLs express a constellation of common T-cell antigens such as CD2, CD3, CD5, and CD7. One or more of these antigens, however, is often not expressed, particularly CD5 or CD7.[11] More PTCLs will express CD4 (T-helper phenotype) than CD8 (cytotoxic phenotype), but some may express both or neither.[12] B-cell antigens such as CD20 or PAX5 are generally absent but have been reported in rare cases.[13]

**Table 2.** Relative Frequency of Peripheral T-Cell Lymphoma (PTCL) Subtypes

| Subtype | Relative Frequency Compared with All Diagnoses of NHL, % |
|---|---|
| PTCL-NOS | 3.7 |
| Anaplastic T/null large cell lymphoma | 2.4 |
| Extranodal NK/T-cell lymphoma, nasal type | 1.4 |
| Angioimmunoblastic T-cell lymphoma with dysproteinemia | 1.2 |
| Others | < 1 |

NHL = non-Hodgkin lymphoma; NOS = not otherwise specified.

Unlike B-cell lymphomas, there are few cytogenetic abnormalities characteristic of most PTCL subtypes. The general lack of recurring cytogenetic abnormalities in PTCL eliminates a valuable diagnostic tool.[14]

Approximately 85% of PTCL cases will have a clonal TCR gene rearrangement.[15] The presence or absence of a clonal TCR rearrangement does not definitively establish or exclude the diagnosis of PTCL and must be considered in the broader clinicopathologic context. Clonal TCR gene rearrangements have been reported in autoimmune and infectious conditions.[16–18]

**Table 3.** Prognostic Indices in Aggressive Lymphomas

| IPI Score | B-Cell NHL 5-Year OS, % | B-Cell NHL (RIPI) 4-Year OS, % | T-Cell NHL 5-Year OS, % |
|---|---|---|---|
| 0 or 1 | 73 | 94 (0) | 74 |
| 2 | 51 | 80 (1–2) | 49 |
| 3 | 43 | 55 | 21 |
| 4 or 5 | 26 | 55 | 6 |

IPI = International Prognostic Index; NHL = non-Hodgkin lymphoma; OS = overall survival; RIPI = Revised International Prognostic Index.

## PREDICTORS OF OUTCOME

With the exception of anaplastic lymphoma kinase (ALK)-positive ALCL, the treatment outcomes for PTCL are generally inferior to those of aggressive B-cell NHLs. The International Prognostic Index (IPI) was developed to predict outcome in diffuse large B-cell lymphoma.[19] The scale assigns 1 point to each of 5 potential risk factors: age greater than 60 years, elevated serum LDH, performance status greater than 2, more than 1 extranodal site of involvement, and stage III/IV disease. The IPI has since been revised (RIPI) to reflect outcome in the post-rituximab era.[20] The IPI is also predictive in PTCL.[21] **Table 3** shows the relative outcome by score on the IPI for aggressive B- and T-cell NHL as well as the corresponding outcome on the RIPI for aggressive B-cell lymphomas. In the pre-rituximab era, the outcome for patients with low- and intermediate-risk IPI scores (0–2) was nearly identical in B- and T-cell lymphoma, while PTCL patients with high-risk IPI scores (3–5) had substantially worse outcomes. Unfortunately, a higher proportion of patients with PTCL will present with a high IPI score relative to aggressive B-cell lymphoma patients.[22] When we consider the RIPI, however, it is now clear that aggressive B-cell lymphoma patients have a markedly superior outcome across all IPI scores relative to patients with PTCL.

**Table 4.** PTCL Outcomes by PIT Score

| PIT Score | 5-Year OS, % | 10-Year OS, % |
|---|---|---|
| 0 | 62 | 55 |
| 1 | 53 | 39 |
| 2 | 33 | 18 |
| 3 or 4 | 18 | 12 |

OS = overall survival; PIT = Prognostic Index for PTCL.

Recently, a separate prognostic index for PTCL (PIT) has been proposed.[23] This model is quite similar to the IPI but includes only 4 factors: age greater than 60 years, performance status of 2 or greater, increased LDH level, and bone marrow involvement. **Table 4** shows the outcome by PIT score. Although the PIT is occasionally cited in clinical papers, the IPI remains the most commonly utilized prognostic index in PTCL.

## DESCRIPTION OF SUBTYPES

### PERIPHERAL T-CELL LYMPHOMA–NOS

PTCL-NOS is a heterogenous disease encompassing PTCLs that do not fit diagnostic criteria for the other defined histologies.[24] Most patients with PTCL-NOS are aged 60 years or older and present with advanced stage disease.[6] PTCL-NOS expresses CD2 and CD3 in most cases. Approximately 50% of cases express CD4, while only about 15% express CD8. CD5, a pan T-cell marker expressed by all mature T cells, and CD7 are each expressed in only about 20% to 50% of cases, and loss of one or both of these antigens should make the clinician suspect a neoplastic rather than a reactive process.[25] EBV early RNA is expressed in about 40% of cases and may confer a worse prognosis.[26] The pathophysiologic importance of EBV in PTCL-NOS is unclear.

There are no characteristic morphologic features of PTCL-NOS. Many cases have cytogenetic

abnormalities, but none are pathognomonic.[27] Although some gene expression–profiling studies can distinguish PTCL-NOS from ALCL and AILT, and in some cases have stratified PTCL-NOS into various subcategories and risk groups, these results need to be validated before they can be applied routinely in the clinical setting.[28] There are morphologic variants of PTCL-NOS such as follicular and lymphoepithelioid (Lennert's lymphoma), but these are of no known clinical consequence.[29,30]

The treatment of PTCL is largely extrapolated from aggressive B-cell malignancies. Most PTCL treatment regimens have utilized an anthracycline and alkylating agent backbone, with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) being the most common. Overall response rates with CHOP have typically ranged between 50% and 70%.[31] In comparison, response rates with CHOP or CHOP-rituximab in B-cell malignancies are generally 80% to 90%.[32] Responses in PTCL are also less durable. The median progression-free survival (PFS) in PTCL following CHOP chemotherapy is 12 to 14 months, with a 5-year disease-free survival (DFS) of approximately 20%.[33] The PFS at 5 years in diffuse large B-cell lymphoma is 54% and long-term DFS is 60%.[32]

Several studies, mostly retrospective, have suggested a benefit from autologous stem cell transplantation (ASCT) in first remission in PTCL-NOS.[34] The National Cancer Control Network (NCCN) suggests that patients with a high IPI score should be considered for ASCT in first remission. Allogeneic stem cell transplant has also been studied in PTCL in the relapsed/refractory setting, but the role and timing of this procedure in PTCL-NOS remains undefined.[35] Ideally, transplantation should occur in the context of a well-designed clinical trial.

## ANAPLASTIC T/NULL LARGE CELL LYMPHOMA

ALCL was first described as a clinical entity in 1985 based upon its unique characteristic of cohesive proliferation of large pleomorphic cells with a horseshoe-shaped or embryoid nucleus expressing CD30 (Ki-1).[36] Between 40% and 60% of cases of ALCL have a translocation between chromosome 2 and chromosome 5 [t(2;5)(p23;q35)],[37] resulting in the fusion of the nucleophosmin (NPM) gene on chromosome 5 with the cytoplasmic domain of ALK on chromosome 2. The subsequent NPM-ALK fusion protein is constitutively active and results in malignant transformation and resistance to apoptosis.[38] Adult patients with ALK-positive ALCL tend to be young men (median age 34 years) and have a more favorable prognosis, while patients with ALK-negative ALCL tend to be older and tend to follow a more aggressive course.[39]

The majority of ALCL express one or more T-cell associated antigens, but approximately 40% express neither T- nor B-cell antigens (the "null" phenotype). ALCL with the null phenotype will often, however, have a clonal TCR gene rearrangement.[40] CD45, which is positive on most lymphoid tumors, is occasionally absent. ALCL can be confused morphologically with Hodgkin lymphoma, which is compounded by the fact that both Hodgkin lymphoma and ALCL express CD30.[36] However, CD15, which is frequently expressed in Hodgkin lymphoma, is rarely positive in ALCL.[41] Another unusual feature of systemic (but not cutaneous, see below) ALCL is the expression of epithelial membrane antigen (EMA), which is not typically seen in lymphoid tumors.[42]

Variant translocations other than t(2;5) occur in up to 15% to 20% of cases.[43] These include t(1;2)(q25;p23), inv(2)(p23;q35), t(2;3), and a CLTC (clathrin heavy chain)-ALK fusion transcript

**Table 5.** Treatment Outcomes for ALCL

| Investigator | ALK-Positive 5-Year OS, % | ALK-Negative 5-Year OS, % |
|---|---|---|
| Shiota et al[56] | 80 | 33 |
| Nakamura et al[57] | 72 | 30 |
| Falini et al[43] | 71 | 15 |
| Gascoyne et al[58] | 93 | 37 |
| Savage et al[59] | 70 | 49 |

ALK = anaplastic lymphoma kinase; OS = overall survival.

typically resulting from a t(2;17) translocation.[44] The prognosis of patients with variant translocations is similar to that of patients with the classic t(2;5) translocation.[45] ALK-negative ALCL shows recurrent chromosomal gains in 46% of cases, with losses of 6q and 13q both occurring in 23% of cases.[46] The pathogenic and prognostic significance of these chromosomal alterations is unknown.

ALCL has a peak incidence in childhood and accounts for approximately 40% of NHL cases diagnosed in pediatric populations.[47] There is a male predominance, particularly in ALK-positive cases.[48] There are no clear risk factors for developing ALCL.[33] Some reports have suggested that EBV is important in the pathogenesis of ALCL; however, recent studies have refuted this.[49] ALCL occurs as 2 distinct clinical entities, a primary cutaneous (PCALCL) and a systemic variant.[50] Primary cutaneous ALCL is indolent with disease-specific survivals at 5 and 10 years of 85% or better.[51] Approximately 10% of patients will develop systemic ALCL, usually in lymph nodes draining areas of skin involvement.[52] Curiously, the prognosis of patients with secondary spread to lymph nodes or with multifocal lesions appears to be no worse than that of patients with solitary lesions.[53]

PCALCL can be confused with systemic ALCL, which frequently involves the skin. Thus, all patients with PCALCL should have complete staging with computed tomography scans, bone marrow biopsy, and a complete blood count to rule out systemic involvement. One useful distinction is the fact that PCALCL rarely has t(2;5) or variant translocations and therefore generally does not express ALK, whereas systemic ALCL often does.[32]

In contrast to PCALCL, systemic ALCL is generally aggressive. Most patients present with advanced stage disease and have systemic symptoms.[54] Extranodal disease occurs in 40% to 60% of patients, with skin, bone, soft tissue, and lung being common sites of involvement.[44,55] **Table 5** lists several series examining the outcome of ALCL with anthracycline-based chemotherapy.[43,56–59]

Due to the superior outcome of ALK-positive ALCL, this variant is generally excluded from most upfront treatment trials in PTCL. The initial treatment of ALK-negative ALCL usually consists of CHOP. The role of ASCT in first remission is unclear but appears to improve outcome in some series.[60] ASCT should be considered in first complete remission for patients with ALK-negative ALCL who have an intermediate or high IPI score.

### ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

AILT presents in older patients, with a median age at diagnosis of 60 years. There is a slight male predominance. Adenopathy, generalized rash, fevers, and night sweats are common.[61] Polyclonal gammopathy is also common. Patients often develop associated autoimmune phenomenon such as hemolytic anemia, arthritis, cryoglobulinemia, and thyroid abnormalities.[62] Rarely AILT spontaneously remits, but more commonly it follows a very aggressive course.[63]

Morphologic analysis shows effaced nodal architecture, open peripheral sinuses, and prominent arborizing high endothelial venules with numerous follicular dendritic cells surrounding proliferating blood vessels.[64] AILT has a follicular T-helper lymphocyte immunophenotype and CXCL13, PD1 and vascular endothelial growth factor expression.[65] A small proportion of AILT will have a clonal B-cell infiltrate, and both the B cells and malignant T cells can show involvement with human herpes virus 6 (HHV-6) or EBV.[66] The pathophysiologic significance of EBV and HHV-6 is unknown. Occasionally, patients with AILT will also develop EBV-positive secondary B-cell lymphomas.[67]

The treatment of AILT is varied. Some patients will respond to prednisone or even cyclosporine, although most are treated with anthracycline-based chemotherapy regimens such as CHOP.[68] In a study comparing CHOP to prednisone, the complete remission rate was 64% with CHOP and 29% with prednisone, with a median survival of 19 months in patients receiving CHOP compared with 11 months in those receiving prednisone.[69]

Outcomes in AILT may be improved by ASCT. In a large retrospective trial, the overall survival of patients undergoing ASCT was 67% at 24 months and 59% at 48 months. Patients who had achieved a complete response prior to transplant had superior outcomes.[70] Although retrospective analyses are fraught with selection bias and other statistical challenges, this study suggests that patients with chemosensitive disease, and particularly patients in complete remission, may benefit from consolidation with ASCT. These findings need to be confirmed in a randomized trial. The NCCN recommends consideration of ASCT in first remission for patients with an intermediate or high IPI score.

Allogeneic stem cell transplantation has been studied in a small number of patients with AILT, including patients who had failed a prior autologous transplant. In one series, the PFS and overall survival following allotransplant for AILT were 53% and 64%, respectively.[71] At present, the optimal role and timing of allogeneic transplant remain to be defined.

## ADULT T-CELL LEUKEMIA/LYMPHOMA

ATLL is associated with HTLV-1, a retrovirus endemic to Japan, the Caribbean, and parts of West Africa and South America that is estimated to infect up to 20 million individuals worldwide.[72] The virus is transmitted through exchange of bodily fluids.[73] Up to 4% of patients infected with HTLV-1 will eventually develop ATLL.[74] The mechanism by which HTLV-1 induces oncogenesis is incompletely understood.[75] ATLL consists of medium-sized lymphocytes with condensed chromatin and hyperlobated nuclei, known as clover leaf or flower cells. There is often a small proportion of blast-like cells with deeply basophilic cytoplasm. The immunophenotype is most often positive for CD2, CD4, CD5, CD25, and CD52. CD7 and CD8 are usually negative, while CD3 is generally dimly expressed.[76] There are no pathognomonic cytogenetic changes.

ATLL is rare in the United States. The median age of diagnosis is in the sixties and African-Americans are at far higher risk than Caucasians.[77] There are 4 types of ATLL: acute, lymphomatous, chronic, and smoldering. The distinction is often made on clinical grounds. Patients with acute ATLL present with systemic symptoms such as fevers and night sweats along with hypercalcemia and a high number of circulating malignant cells. Lymphadenopathy, skeletal involvement, cutaneous involvement, and hepatosplenomegaly are

common. Patients with the lymphomatous variant do not have a significant number of circulating cells but otherwise have a very similar manifestation to patients with the acute variant.[78] The outcome for both the acute and lymphomatous variants is poor, with a median survival of 6 to 9 months; unfortunately, these 2 variants account for approximately 80% of cases of ATLL.[79]

The chronic and smoldering variants of ATLL are much less common, and they have a more favorable course. Patients with the chronic variant may have a mildly to moderately elevated lymphocyte count but rarely have significant lymphadenopathy or organ involvement except for cutaneous involvement.[80] Patients with the smoldering variant generally have skin lesions, only without significant lymphocytosis, lymphadenopathy, or organ involvment.[81] Survival of patients with these variants can range from several to many years, and immediate therapy is often not warranted, especially if the patient is under age 40 years, has a normal LDH level, has a good performance status, and has fewer than 3 sites of involvement.[70]

Young and fit patients with aggressive variants of ATLL are generally treated with aggressive regimens modeled after those used in acute lymphoblastic leukemia, while older patients are generally treated with CHOP or CHOP-like regimens. A randomized trial comparing the vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) regimens to biweekly CHOP in ATLL revealed a high complete response rate with VCAP-AMP-VECP compared with CHOP (40% versus 25%, respectively; $P = 0.020$). There was also a trend in improvement in overall survival at 3 years with VCAP-AMP-VECP (24%) compared with dose-dense CHOP (13%), but the difference was not statistically significant ($P = 0.085$). The durability of response remained poor, with a median duration of 13 months, and VCAP-AMP-VECP had substantially higher toxicity than CHOP.[82] Allogeneic transplantation may be of benefit in first remission, but this remains unclear.[83] Salvage therapy with autologous transplant does not appear to be effective.[84]

### NK/T-CELL LYMPHOMA, NASAL TYPE

NK/TCL typically presents in an aggressive fashion in the upper airway or nasal cavity.[85,86] The disease can also present in other isolated sites such as the gastrointestinal tract or skin or can present in a disseminated fashion.[87] NK/TCL is rare in the United States but is much more common in Southeast Asia. NK/TCL afflicts younger patients, including children, and there is a male predominance.[88] NK/TCL is almost always EBV-positive, and it is presumed that EBV is important in the pathogenesis.[89] High levels of circulating EBV DNA are associated with a worse prognosis.[90]

NK/TCL is characterized by a polymorphous infiltrate composed of normal-appearing small lymphocytes, atypical lymphoid cells of varying size, plasma cells, and occasionally eosinophils and histiocytes. A characteristic feature is invasion of vascular walls.[91] NK/TCL is usually positive for CD56 and CD3 but negative for CD4 and CD8. The tumor cells also express the cytotoxic proteins TIA-1, granzyme B, and perforin.[92] The TCR gene is clonally rearranged in fewer than 20% of cases.[93] Loss of heterozygosity of chromosome 6 is common but not pathognomonic.[94]

In patients with localized disease the standard treatment is radiation therapy to all involved

areas, encompassing all paranasal sinuses, the nasopharynx, and the palate.[95] The dose of radiotherapy utilized to treat extranodal NK/TCL is higher than that utilized for most other lymphomas, with a minimum recommended dose of 50 Gy.[96] The value of chemotherapy in localized disease is unclear, but chemotherapy is generally given.[97] Outcomes appear better if radiotherapy is administered first followed by chemotherapy, although the optimal timing of chemotherapy and radiotherapy remains to be defined.[98]

Patients with disseminated disease typically respond poorly to chemotherapy. The median overall survival for localized disease is approximately 3 years compared with 0.36 years in extranasal cases.[88] The poor outcome with chemotherapy has generated interest in more aggressive approaches such as allogeneic and autologous stem cell transplantation, although the role and timing of these procedures remain to be defined.[99]

## HEPATOSPLENIC T-CELL LYMPHOMA (HSTCL)

HSTCL is an extremely aggressive neoplasm that tends to affect young men. Patients usually present with splenomegaly, thrombocytopenia, and signs and symptoms of liver insufficiency such as jaundice.[100] Bone marrow involvement is very common, but lymphadenopathy generally is not prominent.[101] HSTCL can occur in the setting of immunosuppression, particularly after organ transplantation or with the use of anti-tumor necrosis factor-$\alpha$ therapy for autoimmune diseases.[102,103] HSCTL is comprised of medium-sized lymphoid cells with round nuclei, moderately condensed chromatin, and moderately abundant, pale cytoplasm within the sinusoids of the spleen, liver, and bone marrow. The white pulp of the spleen is usually atrophic, and erythrophagocytosis is often evident in the spleen or marrow.[104] The tumor cells are generally positive for CD2, surface CD3, CD7, and occasionally CD56, while CD4, CD5, and CD8 are usually negative.[105] While most cases of PTCL express the alpha/beta TCR, HSTCL generally expresses the gamma/delta TCR.[106] The most common chromosomal abnormality is isochromosome 7.[107]

HSTCL responds poorly to chemotherapy. In one series, even with aggressive chemotherapy with or without stem cell transplantation, only 50% of patients achieved a complete response and the median duration of complete response was 8 months. Median overall survival was 11 months.[108] Autologous or allogeneic stem cell transplantation may be of benefit either in first remission or at relapse, though most patients will not achieve a remission, particularly in the relapse setting, to benefit from these procedures.[109] All patients with this disease should preferentially be treated in a well-designed clinical trial.

## SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA (SPTCL)

SPTCL is a very rare entity that generally affects young adults.[110] There seems to be a female predominance but no other clear risk factors. Most patients present with subcutaneous nodules mimicking infectious or autoimmune panniculitis.[111] An associated hemophagocytic syndrome (HPS) is common.[112] Often serial biopsies are needed to make the diagnosis.

Previously there were 2 recognized variants of SPTCL, an alpha/beta and a gamma/delta variant. The gamma/delta variant is now reclassified as cutaneous gamma/delta T-cell lymphoma (CGDTCL) in the 2008 WHO classification.[113] SPTCL cells have a cytotoxic phenotype and are CD8-positive but CD4-negative, while CGDTCL is usually CD4-negative and CD8-negative.[114] Morphologically, SPTCL contains a mixture of small, medium,

and large atypical cells, often containing irregular, hyperchromatic nuclei and pale cytoplasm surrounding adipocytes. There are numerous reactive histiocytes with phagocytized nuclear debris and phagocytized lipid from necrotic adipocytes.[111] The malignant cells of SPTCL generally have complex cytogenetic changes, though none are pathognomonic.[115] A small percentage of cases are EBV-positive, although the pathophysiologic and clinical implications of this finding are unclear.[116] Patients with SPTCL often have indolent disease confined to the subcutis and are less likely to have HPS. SPTCL has a favorable prognosis, with a 5-year overall survival of 82% (91% in the absence of HPS). In contrast, patients with CGDTCL more commonly had epidermal involvement and ulceration and were more likely to have HPS. The 5-year overall survival is 11%.[117]

The optimal therapy of SPTCL is unknown. Localized disease may be successfully treated with radiotherapy.[118] Patients with more extensive disease are often initially treated with prednisone,[119] cyclosporine,[120] oral methotrexate,[121] or oral alkylating agents.[122] Nucleoside analogues may also be active.[123] Most patients will eventually require more aggressive systemic chemotherapy, and long-term survivors have been reported after anthracycline-based chemotherapy[124] and after high-dose chemotherapy and ASCT or allogeneic transplantation.[125]

### ENTEROPATHY-TYPE T-CELL LYMPHOMA (EATL)

EATL is a rare condition that occurs most commonly in patients with gluten-sensitive enteropathy (celiac sprue).[126] Most patients with EATL have the HLA DQA1*0501, DQB1*0201 genotype associated with an increased risk of celiac disease.[127] Chronic inflammation due to sustained gluten exposure over time seems to drive the pathogenesis of EATL, and patients who adhere to a gluten-free diet (GFD) have a markedly decreased risk of EATL.[128] Unfortunately, many patients are unaware that they have sprue or are unable to adhere to a GFD. Refractory celiac disease (RCD) occurs when symptoms (eg, diarrhea) and damage to the intestinal mucosa persist despite adherence to a GFD.[129] RCD I is defined as having polyclonal intraepithelial lymphocytes (IELs), while patients with RCD II have a monoclonal, phenotypically aberrant intraepithelial T lymphocyte population that expresses cytoplasmic CD3 but lacks the surface TCR-CD3 complex, possibly due to defective dimerization of the TCR chains and assembly of the TCR-CD3 complex.[130] As many as 50% of RCD II patients will go on to develop EATL, possibly as a result of the loss of TCR gamma/delta-positive IELs that play an important role in mucosal repair, homeostasis, and tumor surveillance.[131]

The average age at diagnosis of EATL is in the late sixth decade, with a male predominance.[124] Patients with EATL often present with rapid-onset abdominal pain, obstruction, or perforation.[132] The small bowel is most commonly affected.[133]

The tumor contains a mixture of different sized malignant lymphocytes that are often anaplastic. The adjacent mucosa generally contains numerous intraepithelial T-cells.[134] Most EATLs have a cytotoxic immunophenotype and are CD3-positive (cytoplasmic expression), CD4- and CD8-negative, and TIA-1-positive.[135] Most EATLs have an alpha/beta TCR gene rearrangement, although gamma/delta cases have been described.[134] Loss of heterozygosity of chromosome 9q21 is a frequent finding, with the region spanning the p14,

p15, and p16 gene locus most frequently affected, leading to decreased p16 protein expression and p53 overexpression.[136] Array comparative genomic hybridization has revealed frequent complex gains of 9q31.3 or loss of 16q12.1. Interestingly, the 2 genomic changes were mutually exclusive, suggesting pathogenetically distinct types of EATL, one which is CD56-negative and affects patients with celiac disease (complex gains in 9q31.3), and a rarer type that is CD56-positive and affects patients with no history of celiac disease (loss of 16q12.1).[137]

EATL is a very aggressive disease. Approximately 10% of patients are long-term survivors, with intestinal perforation and infection being the most common causes of death.[138] Surgery alone is not adequate therapy, even if the patient has no evidence of disease postoperatively.[125] The optimal chemotherapeutic approach is unknown but generally consists of aggressive anthracycline-based chemotherapy regimens such as CHOP.[139] Unfortunately, the response rates with anthracycline-based chemotherapy are low and treatment is often punctuated by life-threatening complications such as infection, intestinal perforation, gastrointestinal bleeding, and/or malnutrition requiring parenteral feeding.[125] The poor outcomes with standard chemotherapy have generated interest in high-dose therapy and autologous or allogeneic stem cell transplantation. Long-term survivors have been reported after stem cell transplantation, but the optimal timing and type of transplant are unclear.[140,141] The NCCN does recommend consolidative ASCT in fit patients who achieve remission with first-line therapy.

### T-CELL PROLYMPHOCYTIC LEUKEMIA (T-PLL)

T-PLL is generally an aggressive disease with an average age of diagnosis in the mid sixties and a male predominance. Most patients present with a rapidly rising lymphocyte count, hepatosplenomegaly, marrow infiltration, and lymphadenopathy.[142] Cutaneous involvement and serous effusions are common.[143] Rarely, T-PLL can follow an indolent course similar to B-cell chronic lymphocytic leukemia.[144]

T-PLL consists of medium-sized cells with moderately condensed chromatin and a single, prominent nucleolus.[143] The neoplastic cells usually strongly express CD7 along with other T-cell markers such as CD2, CD3, and CD5. Most cases are CD4-positive and CD8-negative, though CD4-negative/CD8-positive cases do occur.[145] The majority of cases are also CD52-positive.[146] The most common chromosomal abnormality in T-PLL is inv(14)(q11;q32), which is present in the majority of cases.[147] This translocation juxtaposes the TCR alpha gene (14q11) to the oncogene TCL1 (14q32).[148] TCL1 can modulate the activity of the serine-threonine kinase AKT, a downstream effector of TCR signaling, which can lead to cell proliferation and growth.[149] T-PLL is the most common form of leukemia found in older children with ataxia-telangiectasia, which implicates the ATM tumor suppressor gene in the pathogenesis of T-PLL.[150] In fact, molecular analysis has revealed that mutations of the ATM gene are common in sporadic T-PLL, although chromosome 11, on which ATM is carried, is usually normal on routine cytogenetic analysis.[151] A less common translocation is t(X;14), which again involves the TCR alpha gene, but in this instance it is juxtaposed to the MTCP-1 gene, which is homologous to ATM (Xq28).[152]

T-PLL responds poorly to chemotherapy. Nucleoside analogues such as fludarabine and pentostatin have been utilized with some success.[153] Perhaps the most effective therapy for T-PLL is the anti-CD52 monoclonal antibody alemtu-

zumab. Alemtuzumab single-agent therapy has a response rate of approximately 75% and is considered by many to be the standard initial therapy for T-PLL.[154] Unfortunately the median duration of remission is only 7 months. Allogeneic stem cell transplantation should be considered in patients with T-PLL who achieve an initial remission with either a nucleoside analogue or alemtuzumab. Although the data are limited, long-term survivors have been reported.[155]

### T-CELL LARGE GRANULAR LYMPHOCYTIC LEUKEMIA (T-LGL)

T-LGL is a very indolent disease, and a substantial portion of patients are asymptomatic at diagnosis. The remainder generally present with recurrent fever and infections involving the skin, sinuses, and perirectal area.[156] Systemic symptoms such as fatigue or weight loss are occasionally present. Most patients are over the age of 60 years at diagnosis, and both sexes are affected equally.[157] The most common peripheral blood findings are neutropenia and a mild lymphocytosis with large granular lymphoctyes.[158] However, patients can present with pancytopenia or even an autoimmune hemolytic anemia.[159]

The etiology of T-LGL is unknown. Transient clonal T-LGL expansions can occur in response to viral infections such as cytomegalovirus, and care must be taken not to overdiagnose T-LGL.[160] Patients with T-LGL are more likely to have serologic evidence of exposure to HTLV-1/2 than controls, but whether there is a causal relationship between T-LGL and HTLV is unclear.[161] In many cases, T-LGL is associated with another underlying condition, most commonly rheumatoid arthritis.[162] Most patients with T-LGL have a positive rheumatoid factor, and a high percentage will also have antinuclear antibodies. Polyclonal gammopathy is also common.[163] T-LGL has been associated with B-cell lymphoproliferative disorders, multiple myeloma, monoclonal gammopathy of undetermined significance, and myelodysplasia.[164]

T-LGL consists of large lymphocytes with abundant cytoplasm and azurophilic granules. The nucleus is round or reniform.[165] The majority of T-LGL cases show a CD3-positive, CD4-negative, CD8-positive, CD16-positive, CD57-positive, CD56-negative phenotype, although CD8-negative cases have been described.[165] A clonal TCR gene rearrangement is generally present and is usually alpha/beta.[166] There is no pathognomonic cytogenetic abnormality.[167] Of note, there is also an NK-variant of LGL accounting for about 15% of cases. These cells are usually CD3-negative and CD56-positive and are often EBV-positive.[168] NK-LGL usually presents in younger patients and is much more aggressive than T-LGL.[169]

Many cases of T-LGL are quite indolent and do not require immediate therapy. One study demonstrated a median survival of greater than 10 years.[170] Treatment is indicated for patients with progressive cytopenias, symptoms (eg, severe night sweats), or recurrent infections due to neutropenia. First-line treatment generally consists of oral methotrexate or oral cyclophosphamide with or without prednisone.[171,172] Relapsed or refractory T-LGL can be treated with cyclosporine or alemtuzumab.[173] Aggressive chemotherapy is occasionally needed.

### AGGRESSIVE NK-CELL LEUKEMIA

Aggressive NK-cell leukemia is an extremely rare disease. The immunophenotype of this disorder is generally positive for CD2, CD3, and CD56 with loss of expression of CD5 and CD7. There is

no characteristic cytogenetic abnormality.[174] The prognosis is poor, with most patients surviving only a few months.[175]

## TREATMENT OF RELAPSED/REFRACTORY PTCL

A detailed discussion of the management of relapsed/refractory PTCL is beyond the scope of this review, but this topic has been reviewed elsewhere.[176] In short, the optimal management of patients with relapsed/refractory PTCL is unknown. Participation in a clinical trial should be strongly encouraged. In lieu of clinical trials, various agents are utilized. Conventional aggressive lymphoma salvage regimens such as ifosfamide, carboplatin, and etoposide (ICE) and dexamethasone, cytarabine, and cisplatin are commonly used.[177,178] Gemcitabine is also widely used either as a single agent or in combination with other cytotoxics, most commonly platinum drugs.[179,180] These regimens can serve as a bridge to autologous or allogeneic transplant in appropriate patients. In contrast to large B-cell lymphoma, the benefit of transplantation in relapsed PTCL has not been defined by randomized trials.[181] The optimal type of transplant is unclear, although the data almost uniformly show that only patients in remission at the time of transplant (either autologous or allogeneic) are likely to benefit from the procedure.[182]

A number of single-agent therapies have also been studied in relapsed/refractory PTCL. Pralatrexate is an antifolate that is actively transported into malignant cells via reduced folate carrier 1 (RFC-1), an oncofetoprotein important in embryogenesis and also expressed in many different tumor types. Pralatrexate is approved by the US Food and Drug Administration for the treatment of relapsed/refractory PTCL.[183] Other agents that have been studied include the interleukin-2/diphtheria toxin fusion protein denileukin diftitox,[184] the anti-CD52 antibody alemtuzumab,[185] and the proteasome inhibitor bortezomib.[186] The optimal patient populations and sequencing of these drugs have not been well studied.

## SUMMARY

PTCLs are challenging diseases to diagnose as a result of clinical presentations that mimic inflammatory or infectious conditions and pathology findings that are frequently nonspecific. The clinician must maintain a high degree of suspicion for these disorders and must be willing to order repeat biopsies over time if the clinical suspicion for PTCL is high in the context of ambiguous pathology findings. Consultation with an expert hematopathologist is often crucial. The optimal treatment for most forms of PTCL is also unclear and too often ineffective. Given the rarity of these diseases, we must study them in aggregate in clinical trials. In reality, this is a very heterogeneous group of diseases that will likely require individualized therapy based upon histology and molecular biology. Existing anthracycline-based chemotherapy has a reasonable initial response rate, but the relapse rate in most histologies remains unacceptably high. There are few long-term disease-free survivors except among patients with ALK-positive ALCL. Both allogeneic and autologous transplantation have demonstrated impressive results, but these have occurred in small groups of highly selected patients. There remains no consensus as to the optimal role or timing of transplant or even as to the optimal type of transplant. In addition, even

if transplant definitively proves to be helpful, there is tremendous need for new and more effective regimens to achieve deep remissions and optimize the results of transplantation. The encouraging fact remains, however, that our understanding of PTCL is rapidly improving, and this will hopefully translate to more effective therapies in the near future.

**BOARD REVIEW QUESTIONS**

**Test your knowledge of this topic. Go to www.turner-white.com and select Hematology from the drop-down menu of specialties.**

## REFERENCES


1. Costello R, Sanchez C, Le Treut T, et al. Peripheral T-cell lymphoma gene expression profiling and potential therapeutic exploitations. 2009; Nov 12. [Epub ahead of print].
2. Swerdlow SH, Campo E, Harris NL, et al; WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (4th ed). Lyon, France: International Agency for Research on Cancer; 2008.
3. Abouyabis AN, Shenoy PJ, Lechowicz MJ, Flowers CR. Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States. Leuk Lymphoma 2008;49:2099–107.
4. Rüdiger T, Weisenburger DD, Anderson JR, et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 2002;13:140–9.
5. Kwong YL, Anderson BO, Advani R, et al. Management of T-cell and natural-killer-cell neoplasms in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 2009;10:1093–101.
6. López-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann Oncol 1998;9:849–55.
7. Arrowsmith ER, Macon WR, Kinney MC, et al. Peripheral T-cell lymphomas: clinical features and prognostic factors of 92 cases defined by the revised European American lymphoma classification. Leuk Lymphoma 2003;44:241–9.
8. El Weshi A, Akhtar S, Mourad WA, et al. T-cell/histiocyte-rich B-cell lymphoma: clinical presentation, management, and prognostic factors: report on 61 patients and review of literature. Leuk Lymphoma 2007;48:1764–73.
9. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768–85.
10. Rosso R, Paulli M, Magrini U, et al. Anaplastic large cell lymphoma, CD30/Ki-1 positive, expressing the CD15/Leu-M1 antigen. Immunohistochemical and morphological relationships to Hodgkin's disease. Virchows Arch A Pathol Anat Histopathol 1990;416:229–35.
11. Picker L, Weiss L, Medeiros L, et al. Immunophenotypic criteria for the diagnosis of non-Hodgkin's lymphoma. Am J Pathol 1987;128:181–201.
12. Rüdiger T, Geissinger E, Müller-Hermelink HK. 'Normal counterparts' of nodal peripheral T-cell lymphoma. Hematol Oncol 2006;24:175–80.
13. Rahemtullah A, Longtine JA, Harris NL, et al. CD20+ T-cell lymphoma: clinicopathologic analysis of 9 cases and a review of the literature. Am J Surg Pathol 2008;32:1593–607.
14. Nelson M, Horsman DE, Weisenburger DD, et al. Cytogenetic abnormalities and clinical correlations in peripheral T-cell lymphoma. Br J Haematol 2008;141:461–9.
15. Tan BT, Seo K, Warnke RA, Arber DA. The frequency of immunoglobulin heavy chain gene and T-cell receptor gamma-chain gene rearrangements and Epstein-Barr virus in ALK+ and ALK- anaplastic large cell lymphoma and other peripheral T-cell lymphomas. J Mol Diagn 2008;10:502–12.
16. Choi TS, Doh KS, Kim SH, et al. Clinicopathological and genotypic aspects of anticonvulsant-induced pseudolymphoma syndrome. Br J Dermatol 2003;148:730–6.
17. Bakakos P, Pickard C, Wong WM, et al. Simultaneous analysis of T cell clonality and cytokine production in rheumatoid arthritis using three-colour flow cytometry. Clin Exp Immunol 2002;129:370–8.
18. Du G, Qiu L, Shen L, et al. Combined megaplex TCR isolation and SMART-based real-time quantitation methods for quantitating antigen-specific T cell clones in mycobacterial infection. J Immunol Methods 2006;308:19–35.
19. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project, N Engl J Med 1993;329:987–40.
20. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007;109:1857–61.
21. Sonnen R, Schmidt WP, Müller-Hermelink HK, Schmitz N. The International Prognostic Index determines the out-

come of patients with nodal mature T-cell lymphomas. Br J Haematol 2005;129:366–72.
22. Ansell SM, Habermann TM, Kurtin PJ, et al. Predictive capacity of the International Prognostic Factor Index in patients with peripheral T-cell lymphoma. J Clin Oncol 1997;15:2296–301.
23. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474–9.
24. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004;15:1467–75.
25. Went P, Agostinelli C, Gallamini A, et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol 2006;24: 2472–9.
26. Dupuis J, Emile JF, Mounier N, et al. Prognostic significance of Epstein-Barr virus in nodal peripheral T-cell lymphoma, unspecified: a Groupe d'Etude des Lymphomes de l'Adulte (GELA) study. Blood 2006;108:4163–9.
27. Ong ST, Le Beau MM. Chromosomal abnormalities and molecular genetics of non-Hodgkin's lymphoma. Semin Oncol 1998;25:447–60.
28. Ballester B, Ramuz O, Gisselbrecht C, et al. Gene expression profiling identifies molecular subgroups among nodal peripheral T-cell lymphomas. Oncogene 2006;25:1560–70.
29. Rodríguez-Pinilla SM, Atienza L, Murillo C, et al. Peripheral T-cell lymphoma with follicular T-cell markers. Am J Surg Pathol 2008;32:1787–99.
30. Patsouris E, Engelhard M, Zwingers T, Lennert K. Lymphoepithelioid cell lymphoma (Lennert's lymphoma): clinical features derived from analysis of 108 cases. Br J Haematol 1993;84:346–8.
31. Schmitz N, Ziepert M, Nickelsen M, et al. T-cell lymphomas in studies of the German High-grade NHL study group (DSHNHL) [abstract]. Ann Oncol 2008;9 Supp 4:94a.
32. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117–26.
33. Armitage J, Vose J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124–30.
34. Reimer P, Rüdiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol 2009;27:106–13.
35. de Lavallade H, Cassier PA, Bouabdallah R, et al. Sustained response after reduced-intensity conditioning allogeneic stem cell transplantation for patients with relapsed peripheral T-cell non-Hodgkin lymphoma. Br J Haematol 2008;142: 848–50.
36. Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985;66:848–58.
37. Downing JR, Shurtleff SA, Zielenska M. Molecular detection of the (2; 5) translocation of non-Hodgkin's lymphoma by reverse transcriptase-polymerase chain reaction. Blood 1995;85:3416–22.
38. Ambrogio C, Martinengo C, Voena C, et al. NPM-ALK oncogenic tyrosine kinase controls T-cell identity by transcriptional regulation and epigenetic silencing in lymphoma cells. Cancer Res 2009;69:8611–9.
39. de Bruin PC, Beljaards RC, van Heerde P, et al. Differences in clinical behaviour and immunophenotype between primary cutaneous and primary nodal anaplastic large cell lymphoma of T- or null cell phenotype. Histo Pathol 1993;23:127–35.
40. Kutok JL, Aster JC. Molecular biology of anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma. J Clin Oncol 2002;20:3691–702.
41. Juco J, Holden JT, Mann KP, et al. Immunophenotypic analysis of anaplastic large cell lymphoma by flow cytometry. Am J Clin Pathol 2003;119:205–12.
42. Vassallo J, Lamant L, Brugieres L, et al. ALK-positive anaplastic large cell lymphoma mimicking nodular sclerosis Hodgkin's lymphoma: report of 10 cases. Am J Surg Pathol 2006;30:223–9.
43. Falini B, Bigerna B, Fizzotti M, et al. ALK expression defines a distinct group of T/null lymphomas ("ALK lymphomas") with a wide morphological spectrum. Am J Pathol 1998;153:875–86.
44. Wlodarska I, De Wolf-Peeters C, Falini B, et al. The cryptic inv(2) (p23q35) defines a new molecular genetic subtype of ALK-positive ALCL. Blood 1998;92:2688–95.
45. Pulford K, Lamant L, Morris S, et al. Detection of ALK and NPM-ALK protein in normal and neoplastic cells with the monoclonal antibody ALK1. Blood 1997;89:1394-404.
46. Falini B, Pulford K, Pucciarini A, et al. Lymphomas expressing ALK rusion protein(s) other than NPM-ALK. Blood 1999;94:3509–15.
47. Sandlund JT, Pui CP, Santana VM, et al. Clinical features and treatment outcome for children with CD30+ large cell non-Hodgkin's lymphoma. J Clin Oncol 1994; 12:895–8.

48. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinicopathological findings and outcome. Blood 1999;93:2697–706.
49. Herling M, Rassidakis GZ, Jones D, et al. Absence of Epstein-Barr virus in anaplastic large cell lymphoma: a study of 64 cases classified according to World Health Organization criteria. Human Pathol 2004;35:455–9.
50. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. Blood 1994;84:1361–92.
51. Liu HL, Hoppe RT, Kohler S, et al. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Acad Am Dermatol 2003;49:1049–58.
52. Bekkenk M, Geelen FAMJ, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30-positive lymphoproliferative disorders: long term follow-up data of 219 patients and guidelines for diagnosis and treatment: a report from the Dutch Cutaneous Lymphoma Group. Blood 2000;95:3653–61.
53. Cabanillas F, Armitage J, Pugh WC, et al. Lymphomatoid papulosis: a T-cell dyscrasia with a propensity to transform into malignant lymphoma. Ann Intern Med 1995;122:210–7.
54. Kadin ME, Carpenter C. Systemic and primary cutaneous anaplastic large cell lymphomas. Semin Hematol 2003;40:244–56.
55. Noorduyn LA, van Heerde P, Meyer CJ. Cytology of Ki-1 (CD-30) positive large cell lymphoma. Cytopathology 1990;1:297–304.
56. Shiota M, Nakamura S, Ichinohasama R, et al. Anaplastic large cell lymphomas expressing the novel chimeric protein p80NPM/ALK: a distinct clinicopathologic entity. Blood 1995;86:1954–60.
57. Nakamura S, Shiota M, Nakagawa A, et al. Anaplastic large cell lymphoma: a distinct molecular pathologic entity: a reappraisal with special reference to p80(NPM/ALK) expression. Am J Surg Pathol 1997;21:1420–32.
58. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913–21.
59. Savage KJ, Harris NL, Vose JM. ALK-anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496–504.
60. Chen AI, McMillan A, Negrin RS, et al. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. Biol Blood Marrow Transplant 2008;14:741–7.
61. Alizadeh AA, Advani RH. Evaluation and management of angioimmunoblastic T-cell lymphoma: a review of current approaches and future strategies. Clin Adv Hematol Oncol 2008;6:899–909.
62. Siegert W, Nerl C, Agthe A, et al. Angioimmunoblastic lymphadenopathy (AILD)-type T-cell lymphoma: prognostic impact of clinical observations and laboratory findings at presentation. The Kiel Lymphoma Study Group. Ann Oncol 1995;6:659–64.
63. Lachenal F, Berger F, Ghesquières H, et al. Angioimmunoblastic T-cell lymphoma: clinical and laboratory features at diagnosis in 77 patients. Medicine (Baltimore) 2007;86:282–92.
64. Khokhar FA, Payne WD, Talwalkar SS, et al. Angioimmunoblastic T-cell lymphoma in bone marrow: a morphologic and immunophenotypic study. Hum Pathol 2010;41:79–87.
65. Iqbal J, Weisenburger DD, Greiner TC, et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood 2009; Nov 18. [Epub ahead of print].
66. Zhou Y, Attygalle AD, Chuang SS, et al. Angioimmunoblastic T-cell lymphoma: histological progression associates with EBV and HHV6B viral load. Br J Haematol 2007;138:44–53.
67. Willenbrock K, Bräuninger A, Hansmann ML. Frequent occurrence of B-cell lymphomas in angioimmunoblastic T-cell lymphoma and proliferation of Epstein-Barr virus-infected cells in early cases. Br J Haematol 2007;138:733–9.
68. Advani R, Horwitz S, Zelenetz A, Horning SJ. Angioimmunoblastic T cell lymphoma: treatment experience with cyclosporine. Leuk Lymphoma 2007;48:521–5.
69. Siegert W, Agthe A, Griesser H, et al. Treatment of angioimmunoblastic lymphadenopathy (AILD)-type T-cell lymphoma using prednisone with or without the COPBLAM/IMVP-16 regimen. A multicenter study. Kiel Lymphoma Study Group. Ann Intern Med 1992;117:364–70.
70. Kyriakou C, Canals C, Goldstone A, et al. High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2008;26:218–24.
71. Kyriakou C, Canals C, Finke J, et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2009;27:3951–8.
72. Ragin C, Edwards R, Heron DE, et al. Prevalence of

cancer-associated viral infections in healthy afro-Caribbean populations: a review of the literature. Cancer Invest 2008;26:936–47.
73. Eshima N, Iwata O, Iwata S, et al. Age and gender specific prevalence of HTLV-1. J Clin Virol 2009;45:135–8.
74. Proietti FA, Carneiro-Proiettia B, Catalan-Soares BC, Murphy EL. Global epidemiology of HTLV-I infection and associated diseases. Oncogene 2005;24:6058–68.
75. Yoshida M. Multiple viral strategies of HTLV-1 for dysregulation of cell growth control. Annu Rev Immunol 2001;19:475–96.
76. Matutes E. Adult T-cell leukaemia/lymphoma. J Clin Pathol 2007;60:1373–7.
77. Yamamoto JF, Goodman MT. Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997–2002. Cancer Causes Control 2008;19:379–90.
78. Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol 2009;27:453–9.
79. Suzumiya J, Ohshima K, Tamura K, et al. The International Prognostic Index predicts outcome in aggressive adult T-cell leukemia/lymphoma: analysis of 126 patients from the International Peripheral T-cell Lymphoma Project. Ann Oncol 2009 Jan 15. [Epub ahead of print].
80. Bittencourt AL, Barbosa HS, Vieira MD, Farré L. Adult T-cell leukemia/lymphoma (ATL) presenting in the skin: clinical, histological, and immunohistochemical features of 52 cases. Acta Oncol 2009;48:598–604.
81. Shirono K, Hattori T, Hata H, et al. Profiles of expression of activated cell antigens on peripheral blood and lymph node cells from different clinical stages of adult T-cell leukemia. Blood 1989;73:1664–71.
82. Tsukasaki K, Utsunomiya A, Fukuda H, et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 2007;25:5458–64.
83. Shiratori S, Yasumoto A, Tanaka J, et al. A retrospective analysis of allogeneic hematopoietic stem cell transplantation for adult T cell leukemia/lymphoma (ATL): clinical impact of graft-versus-leukemia/lymphoma effect. Biol Blood Marrow Transplant 2008;14:817–23.
84. Phillips AA, Willim RD, Savage DG, et al. A multi-institutional experience of autologous stem cell transplantation in North American patients with human T-cell lymphotropic virus type-1 adult T-cell leukemia/lymphoma suggests ineffective salvage of relapsed patients. Leuk Lymphoma 2009;50:1039–42.
85. Pagano L, Gallamini A, Trape G, et al. NK/T-cell lymphomas 'nasal type': an Italian multicentric retrospective survey. Ann Oncol 2006;17:794–800.
86. Oshimi K, Kawa K, Nakamura S, et al. NK-cell neoplasms in Japan. Hematology 2005;10:237–45.
87. Chan JK, Sin VC, Wong KF, et al. Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood 1997;89:4501–13.
88. Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood 2009;113:3931–7.
89. Wu X, Li P, Zhao J, et al. A clinical study of 115 patients with extranodal natural killer/T-cell lymphoma, nasal type. Clin Oncol (R Coll Radiol) 2008;20:619–25.
90. Lei KI, Chan LY, Chan WY, et al. Diagnostic and prognostic implications of circulating cell-free Epstein-Barr virus DNA in natural killer/T-cell lymphoma. Clin Cancer Res 2002;1:29–34.
91. Kuo TT, Shih LY, Tsang NM. Nasal NK/T-cell lymphoma in Taiwan: a clinicopathologic study of 22 cases, with analysis of histologic subtypes, Epstein-Barr virus LMP-1 gene association, and treatment modalities. Int J Surg Pathol 2004;12:375–87.
92. Ko YH, Ree HJ, Kim WS, et al. Clinicopathologic and genotypic study of extranodal nasal-type natural killer/T-cell lymphoma and natural killer precursor lymphoma among Koreans. Cancer 2000;89:2106–16.
93. Ko YH, Cho EY, Kim JE, et al. NK and NK-like T-cell lymphoma in extranasal sites: a comparative clinicopathological study according to site and EBV status. Histopathology 2004;44:480–9.
94. Sun HS, Su IJ, Lin YC, et al. A 2.6 Mb interval on chromosome 6q25.2-q25.3 is commonly deleted in human nasal natural killer/T-cell lymphoma. Br J Haematol 2003; 122:590–9.
95. Isobe K, Uno T, Tamaru J, et al. Extranodal natural killer/T-cell lymphoma, nasal type: the significance of radiotherapeutic parameters. Cancer 2006;106:609–15.
96. Sakata K, Fuwa N, Kodaira T, et al. Analyses of dose-response in radiotherapy for patients with mature T/NK-cell lymphomas according to the WHO classification. Radiother Oncol 2006;79:179–84.
97. Li YX, Yao B, Jin J, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol 2006;24:181–9.
98. Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008;70:166–74.
99. Lee J, Au WY, Park MJ, et al. Autologous hematopoietic

stem cell transplantation in extranodal natural killer/T cell lymphoma: a multinational, multicenter, matched controlled study. Biol Blood Marrow Transplant 2008;14:1356–64.
100. Gumbs AA, Zain J, Neylon E, et al. Importance of early splenectomy in patients with hepatosplenic T-cell lymphoma and severe thrombocytopenia. Ann Surg Oncol 2009;16:2014–7.
101. Belhadj K, Reyes F, Farcet JP, et al. Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. Blood 2003;102:4261–9.
102. Mackey AC, Green L, Leptak C, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease: update. J Pediatr Gastroenterol Nutr 2009;48:386–8.
103. Roelandt PR, Maertens J, Vandenberghe P, et al. Hepatosplenic gammadelta T-cell lymphoma after liver transplantation: report of the first 2 cases and review of the literature. Liver Transpl 2009;15:686–92.
104. Vega F, Medeiros LJ, Gaulard P. Hepatosplenic and other gammadelta T-cell lymphomas. Am J Clin Pathol 2007;127:869–80.
105. Krenacs L, Smyth MJ, Bagdi E, et al. The serine protease granzyme M is preferentially expressed in NK-cell, gamma delta T-cell, and intestinal T-cell lymphomas: evidence of origin from lymphocytes involved in innate immunity. Blood 2003;101:3590–3.
106. Macon WR, Levy NB, Kurtin PJ, et al. Hepatosplenic alphabeta T-cell lymphomas: a report of 14 cases and comparison with hepatosplenic gammadelta T-cell lymphomas. Am J Surg Pathol 2001;25:285–96.
107. Wlodarska I, Martin-Garcia N, Achten R, et al. Fluorescence in situ hybridization study of chromosome 7 aberrations in hepatosplenic T-cell lymphoma: isochromosome 7q as a common abnormality accumulating in forms with features of cytologic progression. Genes Chromosomes Cancer 2002;33:243–51.
108. Falchook GS, Vega F, Dang NH, et al. Hepatosplenic gamma-delta T-cell lymphoma: clinicopathological features and treatment. Ann Oncol 2009;20:1080–-5.
109. Konuma T, Ooi J, Takahashi S, et al. Allogeneic stem cell transplantation for hepatosplenic gammadelta T-cell lymphoma. Leuk Lymphoma 2007;48:630–2.
110. Gallardo F, Pujol RM. Subcutaneous panniculitic-like T-cell lymphoma and other primary cutaneous lymphomas with prominent subcutaneous tissue involvement. Dermatol Clin 2008;26:529–40, viii.
111. Parveen Z, Thompson K. Subcutaneous panniculitis-like T-cell lymphoma: redefinition of diagnostic criteria in the recent World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas. Arch Pathol Lab Med 2009;133: 303–8.
112. Koh MJ, Sadarangani SP, Chan YC, et al. Aggressive subcutaneous panniculitis-like T-cell lymphoma with hemophagocytosis in two children (subcutaneous panniculitis-like T-cell lymphoma). J Am Acad Dermatol 2009;61:875–81.
113. Kao GF, Resh B, McMahon C, et al. Fatal subcutaneous panniculitis-like T-cell lymphoma gamma/delta subtype (cutaneous gamma/delta T-cell lymphoma): report of a case and review of the literature. Am J Dermatopathol 2008;30:593–9.
114. Kong YY, Dai B, Kong JC, et al. Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathologic, immunophenotypic, and molecular study of 22 Asian cases according to WHO-EORTC classification. Am J Surg Pathol 2008;32:1495–502.
115. Hahtola S, Burghart E, Jeskanen L, et al. Clinicopathological characterization and genomic aberrations in subcutaneous panniculitis-like T-cell lymphoma. J Invest Dermatol 2008;128:2304–9.
116. Harada H, Iwatsuki K, Kaneko F. Detection of Epstein-Barr virus genes in malignant lymphoma with clinical and histologic features of cytophagic histiocytic panniculitis. J Am Acad Dermatol 1994;31:379–83.
117. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111:838–45.
118. Salhany KE, Macon WR, Choi JK, et al. Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotypic analysis of alpha/beta and gamma/delta subtypes. Am J Surg Pathol 1998;22:881–93.
119. Weenig RH, Ng CS, Perniciaro C. Subcutaneous panniculitis-like T-cell lymphoma. Am J Dermatopathol 2001;23:206–15.
120. Rojnuckarin P, Nakorn TN, Assanasen T, et al. Cyclosporin in subcutaneous panniculitis-like T-cell lymphoma. Leuk Lymphoma 2007;48:560–3.
121. Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T cell lymphoma: a systematic analysis of 156 patients reported in the literature. Cancer 2004;101:1404–13.
122. Santucci M, Pimpinelli N, Massi D, et al. Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. Cancer 2003;97:610–27.
123. Chim CS, Loong F, Ng WK, Kwong YL. Use of fludarabine-containing chemotherapeutic regimen results in

durable complete remission of subcutaneous panniculitis-like T-cell lymphoma. Am J Clin Dermatol 2008;9:396–8.
124. Perniciaro C, Zalla MJ, White JW Jr, Menke DM. Subcutaneous T-cell lymphoma. Report of two additional cases and further observations. Arch Dermatol 1993;129:1171–6.
125. Ghobrial IM, Weenig RH, Pittlekow MR, et al. Clinical outcome of patients with subcutaneous panniculitis-like T-cell lymphoma. Leuk Lymphoma 2005;46:703–8.
126. Ekström Smedby K, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood 2008;111:4029–38.
127. Howell WM, Leung ST, Jones DB, et al. HLA-DRB, -DQA, and -DQB polymorphism in celiac disease and enteropathy-associated T-cell lymphoma. Common features and additional risk factors for malignancy. Hum Immunol 1995;43:29–37.
128. Silano M, Volta U, Vincenzi AD, et al. Effect of a gluten-free diet on the risk of enteropathy-associated T-cell lymphoma in celiac disease. Dig Dis Sci 2008;53: 972–6.
129. Rubio-Tapia A, Kelly DG, Lahr BD, et al. Clinical staging and survival in refractory celiac disease: a single center experience. Gastroenterology 2009;136:99–107.
130. Tjon JM, Verbeek WH, Kooy-Winkelaar YM, et al. Defective synthesis or association of T-cell receptor chains underlies loss of surface T-cell receptor-CD3 expression in enteropathy-associated T-cell lymphoma. Blood 2008;112:5103–10.
131. Verbeek WH, Van De Water JM, Al-Toma A, et al. Incidence of enteropathy--associated T-cell lymphoma: a nation-wide study of a population-based registry in the Netherlands. Scand J Gastroenterol 2008;43:1322–8.
132. Gale J, Simmonds PD, Mead GM, et al. Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. J Clin Oncol 2000;18:795–803.
133. Zettl A, deLeeuw R, Haralambieva E, Mueller-Hermelink HK. Enteropathy-type T-cell lymphoma. Am J Clin Pathol 2007;127:701–6.
134. Murray A, Cuevas EC, Jones DB, Wright DH. Study of the immunohistochemistry and T cell clonality of enteropathy-associated T cell lymphoma. Am J Pathol 1995; 14:509–19.
135. De Bruin PC, Connolly CE, Oudejans JJ, et al. Enteropathy associated T-cell lymphomas have a cytotoxic T-cell phenotype. Histopathology 1997;31:313–7.
136. Obermann EC, Diss TC, Hamoudi RA, et al. Loss of heterozygosity at chromosome 9p21 is a frequent finding in enteropathy-type T-cell lymphoma. J Pathol 2004;202:252–62.
137. Deleeuw RJ, Zettl A, Klinker E, et al. Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. Gastroenterology 2007;132:1902–11.
138. Al-Toma A, Verbeek WH, Hadithi M, et al. Survival in refractory coeliac disease and enteropathy-associated T-cell lymphoma: retrospective evaluation of single-centre experience. Gut 2007;56:1373–8.
139. Wohrer S, Chott A, Drach J, et al. Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone (CHOEP) is not effective in patients with enteropathy-type intestinal T-cell lymphoma. Ann Oncol 2004;15:1680–3.
140. Al-Toma A, Verbeek WH, Visser OJ, et al. Disappointing outcome of autologous stem cell transplantation for enteropathy-associated T-cell lymphoma. Dig Liver Dis 2007;39:634–41.
141. Bishton MJ, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. Br J Haematol 2007; 136:111–3.
142. Matutes E, Brito-Babapulle V, Swansbury J, et al. Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia. Blood 1991;78:3269–74.
143. Magro CM, Morrison CD, Heerema N, et al. T-cell prolymphocytic leukemia: an aggressive T cell malignancy with frequent cutaneous tropism. J Am Acad Dermatol 2006;55:467–77.
144. Soma L, Cornfield DB, Prager D, et al. Unusually indolent T-cell prolymphocytic leukemia associated with a complex karyotype: is this T-cell chronic lymphocytic leukemia? Am J Hematol 2002;71:224–6.
145. Dungarwalla M, Matutes E, Dearden CE. Prolymphocytic leukaemia of B- and T-cell subtype: a state-of-the-art paper. Eur J Haematol 2008;80:469–76.
146. Jiang L, Yuan CM, Hubacheck J, et al. Variable CD52 expression in mature T cell and NK cell malignancies: implications for alemtuzumab therapy. Br J Haematol 2009;145:173–9.
147. Bug S, Dürig J, Oyen F, et al. Recurrent loss, but lack of mutations, of the SMARCB1 tumor suppressor gene in T-cell prolymphocytic leukemia with TCL1A-TCRAD juxtaposition. Cancer Genet Cytogenet 2009;192:44–7.
148. Narducci MG, Stoppacciaro A, Imada K, et al. TCL1 is overexpressed in patients affected by adult T-cell leukemias. Cancer Res 1997;57:5452–6.
149. Herling M, Patel KA, Teitell MA, et al. High TCL1 expression and intact T-cell receptor signaling define a hyperproliferative subset of T-cell prolymphocytic leukemia. Blood 2008;111:328–37.
150. Chun HH, Castellví-Bel S, Wang Z, et al. TCL-1, MTCP-1, and TML-1 gene expression profile in non-leukemic clonal

proliferations associated with ataxia-telangiectasia. Int J Cancer 2002;97:726–31.
151. Stoppa-Lyonnet D, Soulier J, Laugé A, et al. Inactivation of the ATM gene in T-cell prolymphocytic leukemias. Blood 1998;91:3920–6.
152. Madani A, Choukroun V, Soulier J, et al. Expression of p13MTCP1 is restricted to mature T-cell proliferations with t(X;14) translocations. Blood 1996;87:1923–7.
153. Mercieca J, Matutes E, Dearden C, et al. The role of pentostatin in the treatment of T-cell malignancies: analysis of response rate in 145 patients according to disease subtype. J Clin Oncol 1994;12:2588–93.
154. Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with Campath-1H. Blood 2001;98:1721–6.
155. de Lavallade H, Faucher C, Fürst S, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in a patient with T-cell prolymphocytic leukemia: graft-versus-tumor effect and long-term remission. Bone Marrow Transplant 2006;37:709–10.
156. Loughran TP Jr, Starkebaum G. Large granular lymphocyte leukemia. Report of 38 cases and review of the literature. Medicine (Baltimore). 1987;66:397–405.
157. Lamy T, Loughran TP Jr. Clinical features of large granular lymphocyte leukemia. Semin Hematol 2003;40:185–95.
158. Mohan SR, Maciejewski JP. Diagnosis and therapy of neutropenia in large granular lymphocyte leukemia. Curr Opin Hematol 2009;16:27–34.
159. Loughran TP Jr, Kadin ME, Starkebaum G, et al. Leukemia of large granular lymphocytes: association with clonal chromosomal abnormalities and autoimmune neutropenia, thrombocytopenia, and hemolytic anemia. Ann Intern Med 1985;102:169–75.
160. Rossi D, Franceschetti S, Capello D, et al. Transient monoclonal expansion of CD8+/CD57+ T-cell large granular lymphocytes after primary cytomegalovirus infection. Am J Hematol 2007;82:1103–5.
161. Duong YT, Jia H, Lust JA, et al. Short communication: absence of evidence of HTLV-3 and HTLV-4 in patients with large granular lymphocyte (LGL) leukemia. AIDS Res Hum Retroviruses 2008;24:1503–5.
162. Shah A, Diehl LF, St Clair EW. T cell large granular lymphocyte leukemia associated with rheumatoid arthritis and neutropenia. Clin Immunol 2009;132:145–52.
163. Bassan R, Pronesti M, Buzzetti M, et al. Autoimmunity and B-cell dysfunction in chronic proliferative disorders of large granular lymphocytes/natural killer cells. Cancer 1989;63:90–5.
164. Huh YO, Medeiros LJ, Ravandi F, et al. T-cell large granular lymphocyte leukemia associated with myelodysplastic syndrome: a clinicopathologic study of nine cases. Am J Clin Pathol 2009;131:347–56.
165. O'Malley DP. T-cell large granular leukemia and related proliferations. Am J Clin Pathol 2007;127:850–9.
166. Bourgault-Rouxel AS, Loughran TP Jr, Zambello R, et al. Clinical spectrum of gammadelta+ T cell LGL leukemia: analysis of 20 cases. Leuk Res 2008;32:45–8.
167. Salido M, Solé F, Espinet B, et al. New t(11;12)(q12;q11) characterized by RxFISH in a patient with T-cell large granular lymphocyte leukemia. Cancer Genet Cytogenet 2001;125:70–3.
168. Loughran TP. Clonal diseases of large granular lymphocytes. Blood 1993;8:1–14.
169. Lamy T, Loughran TP. Large granular lymphocyte leukemia. Cancer Control 1998;5:25–33.
170. Dhodapkar MV, Li CY, Lust JA, et al. Clinical spectrum of clonal proliferations of T-large granular lymphocytes: a T-cell clonopathy of undetermined significance? Blood 1994;84:1620–7.
171. Loughran TP Jr, Kidd PG, Starkebaum G. Treatment of large granular lymphocyte leukemia with oral low-dose methotrexate. Blood 1994;84:2164–70.
172. Kouides PA, Rowe JM. Large granular lymphocyte leukemia presenting with both amegakaryocytic thrombocytopenic purpura and pure red cell aplasia: clinical course and response to immunosuppressive therapy. Am J Hematol 1995;49:232–6.
173. Osuji N, Matutes E, Tjonnfjord G, et al. T-cell large granular lymphocyte leukemia: a report on the treatment of 29 patients and a review of the literature. Cancer 2006;107:570–8.
174. Yoo EH, Kim HJ, Lee ST, et al. Frequent CD7 antigen loss in aggressive natural killer-cell leukemia: a useful diagnostic marker. Korean J Lab Med 2009;29:491–6.
175. Suzuki R, Suzumiya J, Yamaguchi M, et al. Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. Ann Oncol 2009; Oct 22. [Epub ahead of print].
176. Prichard M, Harris T, Williams ME, Densmore JJ. Treatment strategies for relapsed and refractory aggressive non-Hodgkin's lymphoma. Expert Opin Pharmacother 2009;10:983–95.
177. Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14 Suppl 1:i5–10.
178. Tarella C, Cuttica A, Caracciolo D, et al. High-dose sequential (HDS) chemotherapy for high-risk non-Hodgkin's lymphoma: long-term analysis and future developments. Ann Hematol 2001;80 Suppl 3:B123–6.

179. Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 2009; Nov 3. [Epub ahead of print].
180. Arkenau HT, Chong G, Cunningham D, et al. Gemcitabine, cisplatin and methylprednisolone for the treatment of patients with peripheral T-cell lymphoma: the Royal Marsden Hospital experience. Haematologica 2007;92:271–2.
181. Moskowitz AJ, Moskowitz CH. Controversies in the treatment of lymphoma with autologous transplantation. Oncologist 2009;14:921–9.
182. Dreger P, Laport GG. Controversies in lymphoma: the role of hematopoietic cell transplantation for mantle cell lymphoma and peripheral T cell lymphoma. Biol Blood Marrow Transplant 2008;14(1 Suppl 1):100–7.
183. Thompson CA. FDA approves pralatrexate for treatment of rare lymphoma. Am J Health Syst Pharm 2009;66:1890.
184. Dang NH, Pro B, Hagemeister FB, et al. Phase II trial of denileukin diftitox for relapsed/refractory T-cell non-Hodgkin lymphoma. Br J Haematol 2007;136:439–47.
185. Zinzani PL, Alinari L, Tani M, et al. Preliminary observations of a phase II study, reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma. Haematologica 2005;90:702–3.
186. Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293–7.

*The distribution of this publication is made possible through the financial support of Merck*

The Hospital Physician® Board Review Manuals are published by Turner White Communications, Inc., an independent medical publisher dedicated to serving the information and education needs of clinical trainees and practicing physicians.

HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

### STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

### PUBLISHING STAFF

**PRESIDENT, GROUP PUBLISHER**
Bruce M. White

**SENIOR EDITOR**
Robert Litchkofski

**EXECUTIVE VICE PRESIDENT**
Barbara T. White

**EXECUTIVE DIRECTOR OF OPERATIONS**
Jean M. Gaul

**PRODUCTION DIRECTOR**
Jeff White

**NOTE FROM THE PUBLISHER:**
This publication has been developed without involvement of or review by the American Board of Internal Medicine.

# Hemoglobinopathies

**Series Editor:**
**Eric D. Jacobsen, MD**
*Instructor in Medicine, Harvard Medical School; Attending Physician, Dana-Farber Cancer Institute, Boston, MA*

**Contributors:**
**Katharine Batt, MD, MSc**
*Fellow in Hematology/Oncology, Mount Sinai Hospital New York, NY*

**Thomas Reske, MD**
*Fellow in Hematology/Oncology, Boston University Medical Center, Boston, MA*

## Table of Contents



**Cover Illustration by Kathryn K. Johnson**

# Hemoglobinopathies

*Katharine Batt, MD, MSc, and Thomas Reske, MD*

## INTRODUCTION

Hemoglobin is a tetrameric protein composed of 2 pairs of globin chains (4 globin polypeptides) complexed with 4 heme groups. Each globin chain, or subunit, is associated with a heme group in its center. Globin chains are designated as α, β, γ, and δ and are classified as α chain or non–α chain. The dominant form of adult hemoglobin is hemoglobin A (HbA), which is made up of 2 α chains and 2 β chains (**Figure)**.

α-Globin genes are encoded on chromosome 16, and the γ-, δ- and β-globin genes are encoded on chromosome 11. Each individual carries a linked pair of α-globin genes: 2 from the paternal chromosome and 2 from the maternal chromosome. The synthesis and structure of the different globin chains is under tight genetic control, resulting in a 1.00 (± 0.05) ratio of α to non–α chains. Defects in these genes can cause the abnormal production of hemoglobin and anemias, disorders called hemoglobinopathies. These genetic defects can result in structural defects in the hemoglobin molecule, diminished production of the hemoglobin subunits, or abnormal association of subunits. Hemoglobinopathies can be qualitative (abnormal hemoglobin as in sickle cell disease), quantitative (anemia as in thalassemia), or both (sickle cell disease with concurrent thalassemia). Most hemoglobinopathies are not clinically apparent, while others produce abnormal laboratory findings and a few cause serious disease.

Structural defects in the hemoglobin molecule often occur because of mutations in either the α or β subunit chains, but mutations can also appear in the δ and γ chains. The most common clinically encountered qualitative mutation in the United States is hemoglobin S (HbS), a hemoglobinopathy characterized by an amino acid substitution at position 6 on the β chain, resulting in structurally abnormal sickle-shaped hemoglobin.

Mutations that cause diminished production of 1 of the 2 subunits of hemoglobin result in disorders called "thalassemias." Mutations can affect any step in the pathway of globin gene expression, including transcription, pre-mRNA splicing, mRNA translation, mRNA stability, post-translational assembly, and stability of globin polypeptides. The 1.00 ratio of α to non–α chains is not maintained, and there is decreased production of total hemoglobin. Those hemoglobin molecules that are produced are structurally normal. Thalassemias are referred to by the deficient subunit: α-thalas-

**Copyright 2010, Turner White Communications, Inc., Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications. The preparation and distribution of this publication are supported by sponsorship subject to written agreements that stipulate and ensure the editorial independence of Turner White Communications. Turner White Communications retains full control over the design and production of all published materials, including selection of topics and preparation of editorial content. The authors are solely responsible for substantive content. Statements expressed reflect the views of the authors and not necessarily the opinions or policies of Turner White Communications. Turner White Communications accepts no responsibility for statements made by authors and will not be liable for any errors of omission or inaccuracies. Information contained within this publication should not be used as a substitute for clinical judgment.**

semias or β-thalassemias. While the production of normal hemoglobin requires the linking of an α subunit with a β subunit to produce 1 of 2 dimers, in the case of an extreme lack of potential subunit partners, like subunits will abnormally associate. In the case of severe α-thalassemia, the α-globin subunits associate into groups of 4 (tetramers). In severe β thalassemia, α subunits do not self-associate and are rapidly degraded. The amount of affected globin determines the clinical picture and is eponymic for the phenotypes thalassemia minor, thalassemia intermedia, and thalassemia major.

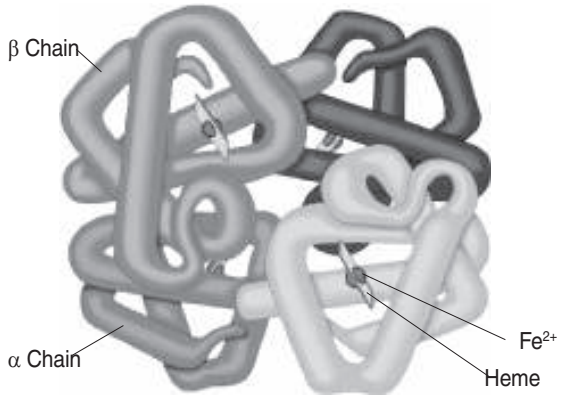



**Figure.** Hemoglobin molecule. (Adapted with permission from themedicalbiochemistrypage.org [http://themedicalbiochemistrypage.org/hemoglobin-myoglobin.html]. Copyright © 1996 Michael W. King, PhD.)

## CLASSIFICATION

Hemoglobinopathies have no universal classification. By convention, hemoglobinopathies are classified according to the qualitative nature of the resultant hemoglobin (ie, sickle cell disease) and the quantitative amount of hemoglobin produced (ie, thalassemia).

The first attempt at classification dates back to the 1950s, when sickle cell hemoglobin was found to migrate differently from normal hemoglobin in an electric field, implying a different ionic charge. *Hemoglobin A*, or HbA, referred to normal adult hemoglobin, and *hemoglobin S*, or HbS, referred to sickle hemoglobin. Fetuses were known to have alkali-resistant hemoglobin, which is referred to as hemoglobin F (HbF). Inherited methemoglobinemia had been described by some Japanese investigators, so M was reserved for such hemoglobin variants. The next variant described was hemoglobin C (HbC), which has 2 more positive charges per tetramer than HbS and therefore migrates more slowly at alkaline pH. Hemoglobins D and G (the latter α variants) migrate in a fashion very similar to HbS. Hemoglobin J and hemoglobin I have 2 and 4 charges per tetramer electronegative to HbA, respectively, and thus migrate faster than HbA. As the discovery of variants continued, it became clear that the alphabet would be exceeded and thus the place of discovery (hemoglobin Edmonton) or the family name of an index case (hemoglobin Lepore) was used.

The advent of sophisticated sequencing technique allows the exact amino acid substitution on the affected chain to be added to the name of the hemoglobin variant. For example, HbS $\alpha_2\beta_2^{6Glu\rightarrow Val}$ indicates that valine is substituted for glutamic acid in the sixth position of the β chain. More than 700 structural hemoglobin variants have been described in the literature.[1] Within these broad categorizations, hemoglobinopathies are often further subdivided by high and low oxygen affinity and physical instability.

Disease manifestation depends largely on the genetic penetrance of the mutation. Heterozygous inheritance often results in either a clinically silent state or mild disease. Homozygous inheritance, however, may be associated with more severe disease. Homozygous hemoglobin variants are referred to as disease; heterozygous vari-

**Table 1.** Commonly Encountered Qualitative Hemoglobin Variants

| Hemoglobin Variants | Position | Substitution |
|---|---|---|
| β Chain | | |
| HbS | 6 | Glutamic acid → Valine |
| HbC | 6 | Glutamic acid → Lysine |
| HbE | 26 | Glutamic acid → Lysine |
| γ Chain | | |
| $HbF_{TexasII}$ | 6 | Glutamic acid → Lysine |

ants are usually termed traits. Homozygous HbC disease is also referred to as hemoglobin CC, while heterozygous HbC trait can be described as hemoglobin AC.

Hemoglobinopathies were traditionally detected on the basis of ionic charge differences imparted by amino acid substitutions; however, certain important variants are electrophoretically silent because the amino acid substitution does not alter the net charge. Quantitation of hemoglobin can provide valuable information as to the hemoglobin variant in question. Hemoglobin $A_2$ ($HbA_2$, consisting of 2 α and 2 δ chain) is most often elevated in β-thalassemia trait and decreased in some α-thalassemias and severe iron deficiency. Combination variants that comigrate with other hemoglobins can be further delineated by isoelectric focusing or high performance chromatography. In qualitative hemoglobinopathies, mutations can appear in any of the 4 different hemoglobin chains. **Table 1** displays representative qualitative hemoglobin chain mutations.

Deoxygenation of the red cells of persons homozygous for the HbS gene results in aggregation of HbS molecules into chains, or microfibrils, that stiffen the red cells and stretch them into the classic sickle shape. In this process, the membranes become permeable to water and potassium, resulting in cellular dehydration. The deranged membranes also interact with adhesion molecules in the plasma, making the sickle cells adhere to one another as well as to the vascular endothelium, thus causing vaso-occlusion. Red cell hemolysis also occurs. End organ damage develops from episodes of intermittent vascular clogging and tissue ischemia. Most of the pain is due to vaso-occlusion of bone, where the low shear forces of sinusoidal blood flow are less apt to disrupt cellular aggregation than in other vascular beds. Inflammation precipitates painful vaso-occlusive episodes. The dilution of HbS by HbA in sickle cell trait makes the red blood cells resistant to sickling at the oxygen tensions prevailing in most parts of the body most of the time. **Table 2** outlines the common clinical and hematologic findings in the common variants of sickle cell disease.

Quantitative hemoglobin disorders, or thalassemias, are classified according to the deficient globin chain. α-Thalassemia results from deletion of 1 or more of the 4 α-chain genes. Any genetic variant that decreases or increases the number of unpaired α chains can modify the phenotype; this applies to compound heterozygotes as well as homozygotes. The severity of disease is directly correlated to the number of genes deleted. Patients with 2 deleted or inactivated α chains present with borderline hypochromic, microcytic anemia, whereas patients with one functional α gene, known as hemoglobin H, have moderate to severe hemolytic anemia. As α chains are present in fetal and adult hemoglobin, α-chain deficiency affects the hemoglobin of both fetuses and adults. Lack of α-chain production altogether is incompatible with life, and affected fetuses are typically stillborn (hydrops fetalis).

The types of β-thalassemia are classified according to their zygosity as either minor (heterozygous) or major (homozygous). The disease

**Table 2.** Clinical and Hematologic Findings in the Common Variants of Adult Sickle Cell Disease

| | Hematologic Value | | | Clinical Severity | Hgb Electrophoresis,% | | | |
|---|---|---|---|---|---|---|---|---|
| **Genotype** | **Hgb, g/dL** | **MCV, fL** | **RBC** | | **S** | **F** | **$A_2$** | **A** |
| AS | 12–15 | > 80 | Normal | None | 40–50 | < 5 | < 3.5 | 50–60 |
| SS | 6–11 | > 80 | Sickle cells, target cells | Moderate to severe | > 85 | 2–15 | < 3.5 | 0 |
| SC | 10–15 | 75–95 | Sickle cells, target cells | Mild to moderate | 50 | 1–8 | < 3.5 | 0 |

Hgb = hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell.

commonly is secondary to point mutations that lead to impaired or absent β-chain synthesis. Mutations that result in complete suppression of the β chain are designated as β0, whereas mutations that result in diminished synthesis are designated as β+. Other thalassemia subtypes are δ and δβ. δ-Thalassemia is characterized by output of a diminished number of δ chains, whereas δβ is associated with suppression of β- and δ-chain synthesis. Rare forms such as homozygous εγδβ thalassemia are incompatible with life, and such mutations have only been observed in heterozygotes.

Variants that present with combined qualitative and quantitative hemoglobin abnormalities are also seen, the most common being sickle/β-thalassemia. The combination of both underlying abnormalities in one genotype is named *compound hemoglobin*. **Table 3** presents a functional overview of the most common quantitative and compound disorders.

**Table 3.** Functional Classification of Quantitative and Combined Hemoglobinopathies

| **Quantitative Disorders (Thalassemia)** | **Globulin Chain Affected** | **Clinical Spectrum** |
|---|---|---|
| α-Thalassemia | Decreased α chains | |
| Normal (100% globulin output) | 4: αα/αα | Normal |
| Silent carrier, 75% | 3: -α/αα | Normal |
| α-Thalassemia trait, 50% | 2: —/αα or -α/-α | Mild hypochromic, microcytic anemia |
| HbH disease, 25% | 1: -α/— | Hemolytic anemia |
| Hydrops fetalis, 0% | 0: —/— | Stillborn, severe anemia |
| β-Thalassemia | Decreased β chains | Clinical spectrum from mild to severe hemolytic anemia |
| β- and δ-chain variants | Decreased β and δ chains | Clinical spectrum of thalassemia-like syndrome |
| **Combined Disorders** | **β Globin Genotype** | **Clinical Spectrum** |
| Sickle/β0-thalassemia | S-β0 | Moderate to severe hemolysis; overlaps with SS in severity |
| Sickle/β+-thalassemia | S-β+ | Mild hemolysis |

- = absent or deleted α chain; — = both genes on the locus deleted; HbH = hemoglobin H; SS = sickle cell disease.

## EPIDEMIOLOGY

Hemoglobinopathies have historically clustered in geographical areas in which malaria is endemic. The assumption is that the HbS mutation conferred a selective advantage for heterozygotes.[2–6] Homozygotes may die of their disease, whereas hemoglobin A/A individuals are more apt to die of malaria. The most genetically fit person in the malaria belt population is the heterozygote. It is estimated that approximately 7% of the world population carry a globin-gene mutation, most frequently inherited as an autosomal recessive trait.[7]

Thalassemias are the most common genetic disorders worldwide.[8] Approximately 15% of African Americans are silent carriers for α-thalassemia; the α-thalassemia trait occurs in 3% of the African-

American population and in 1% to 15% of persons of Mediterranean origin.[3] β-Thalassemia is prevalent in Mediterranean populations (10%–-15% incidence), as well as those from Southeast Asia, West Africa, and the Middle East. It occurs in less than 1% of African Americans.

HbS, HbC, and hemoglobin E (HbE) are the most frequently encountered qualitative hemoglobinopathies. HbS has the greatest prevalence in tropical Africa, with a heterozygous frequency up to 20%. The sickle cell gene has also been reported in the Middle East, Greece, and India, although it occurs in these countries at a markedly lower rate. In the United States, HbS has been reported in 9% of the African-American population.[9] HbC is found in more than 30% of the West African population[10] and has been reported in approximately 3% of African Americans. HbE is found predominantly in Southeast Asia, most commonly in Thailand and Cambodia and less commonly in Malaysia.[3,11]

Through migration, hemoglobinopathies have spread from their native areas and are now endemic throughout Europe, the Americas, and Australia.[12] Although rare, thalassemias can occur in all racial groups due to sporadic mutations; thus, racial background does not preclude the diagnosis.

## CASE PRESENTATION

A 21-year-old man presents to the emergency department with chest pain that started 12 hours ago. He has a diagnosis of HbS/β0 thalassemia. His outpatient medications are hydroxyurea, folate, and oxycodone as needed for pain.

His past medical history is significant for a splenectomy at the age of 5 years, a cholecystectomy at age 8 years, and avascular necrosis of the left femoral head.He also has mild cardiac dysfunction with global left ventricular hypokinesis and an ejection fraction of 50% by recent echocardiography. His last hospitalization was for a pain crisis that occurred 2 years ago.

The patient has no history of smoking, alcohol use, or drug abuse; he is currently enrolled in college and he describes himself as single. His mother is originally from Iran; his father was born in West Africa.

On further questioning, the patient complains of diffuse throbbing chest pain that he ranks as 8/10 on a pain scale. He reports the pain is mostly anterior chest pain and states that his usual sickle cell pain is lower back and joint pain and is relieved by nonsteroidal anti-inflammatory agents. He is afebrile with a pulse of 108 bpm, blood pressure of 135/67 mm Hg, respiratory rate of 21 breaths/min, and an oxygen saturation of 93% on room air.

It is apparent that the patient is in some degree of physical distress, using accessory muscles to breath. His pulmonary exam is significant for crackles at the base of his right lobe. On cardiac auscultation he has a grade III systolic murmur over his right upper sternal border. The remainder of his physical examination is unremarkable.

Results of initial laboratory tests show a white blood cell (WBC) count of 18,100/μL, with a neutrophilia; a hemoglobin level of 7.3 g/dL, down from his baseline of 9 g/dL; a mean corpuscular volume (MCV) of 77 fL, (normal, 80–96 fL); and a platelet count of 424,000/μL (normal, 150,000–400,000/μL). A peripheral blood smear shows microcytosis and polychromatophilia. The patient's urinalysis is normal; blood cultures are negative for bacteria after 48 hours. A chest radiograph shows right basilar opacities.

### CLINICAL PRESENTATION

How a patient presents depends on the characteristics of the underlying hemoglobinopathy.

Mutations or alterations of the globin protein produce pronounced changes in the functional property of hemoglobin, including oxygen affinity and solubility, and impair the structural integrity of the erythrocyte.[13] Heterozygous disorders usually have a benign presentation, whereas homozygous disorders can lead to significant anemia and hemolytic and/or vaso-occlusive crises. Qualitative hemoglobinopathies (eg, homozygous HbS) are characterized by rigid red blood cells that do not pass through capillaries and cause microinfarction or vaso-occlusion, both of which can lead to acute and chronic organ damage. The amount of sickle cells is directly related to the severity of the hemolytic process.[14] That said, sickle cell disease remains a highly phenotypically variable disease. In the steady state, individuals with a qualitative hemoglobinopathy usually present with a normochromic, normocytic anemia in the range of 5 to 11 g/dL. The anemia is usually accompanied by an elevated reticulocyte count and a reduced erythropoietin level relative to the anemia. Laboratory workup is indicative of hemolysis, as indirect serum bilirubin and lactate dehydrogenase (LDH) are elevated.

Current risk stratification for common complications remains incomplete, but certain findings are predictive of outcomes. For example, a low HbF concentration and leukocytosis are associated with increased risk of early death, acute chest syndrome, and painful crises.[15] Higher steady state hemoglobin concentrations are associated with avascular necrosis and sickle cell retinopathy.[16] Compound disease, such as sickle cell/β-thalassemia, presents with a spectrum of clinical manifestations that reflect the underlying chain defect. The severity of disease is an inverse function of the quantity of HbA. Patients with sickle cell/β0 thalassemia have more irreversible sickled cells in the peripheral smear than patients with sickle cell/β+. Both compound sickle cell variants present with clinical manifestations, although they are less severe than those seen with homozygous HbS.

Quantitative and qualitative hemoglobinopathies can present with a similar range of anemia. The majority of patients with α- and β-thalassemia minor are diagnosed because of an asymptomatic microcytic, hypochromic anemia. Anemia can be more pronounced in thalassemias of intermediate degree, while in thalassemia major patients present with life-long transfusion-dependent anemia and iron overload syndromes, which untreated can lead to end organ damage.

**Organ-Specific Findings**

The function of blood and its role in oxygen delivery means that hemoglobinopathies can affect any organ system. Organ findings in hemoglobinopathy reflect the effects of compensatory hemoglobin production, distribution and disposal of hemolyzed red blood cells, and iron deposition, particularly from recurrent transfusions. The most commonly affected organ systems are the cardiopulmonary, renal, and central nervous systems, skin, bone, and the genitourinary, endocrine and the reticuloendothelial systems (**Table 4**).

**Cardiopulmonary** symptoms of shortness of breath and tachycardia secondary to anemia are the most common presenting symptoms of sickle cell disease.[17] Chronic tachycardias can result in ventricular remodeling. In HbS disease, recurrent occlusive crises of the cardiac and pulmonary vasculature result in micro-infarcts that eventually alter blood supply, cardiac workload, and cardiac contractility.[18–20] Fat embolus

**Table 4.** Organ-Specific Findings in Hemoglobinopathies

| Condition | Clinical Abnormalities | Hgb Level, g/dL |
|---|---|---|
| Sickle cell trait | None; rare painless hematuria | Normal |
| Sickle cell anemia | Vaso-occlusive crises with infarction of spleen, brain, marrow, kidney, lung; aseptic necrosis of bone; gallstones; priapism; ankle ulcers | 7–10 |
| S/β0 thalassemia | Same as sickle cell anemia | 7–10 |
| S/β+ thalassemia | Same as sickle cell anemia | 10–14 |
| HbSC | Rare crises and aseptic necrosis; painless hematuria | 10–14 |
| Silent thalassemia: -α/αα | Minimal microcytosis | 15 |
| Thalassemia trait: -α/-α (homozygous α-thal-2[a]) or —/αα heterozygous (α-thal-1[a]) | Similar to β-thalassemia minor; mild anemia; rare blood cell inclusions (precipitated HbH) | 12–13 |
| HbH disease: —/-α (heterozygous α-thal-1/α-thal-2) | Thalassemia intermedia with moderately severe hemolytic anemia; precipitated HbH; transfusions necessary in midlife | 6–10 |
| Hydrops fetalis: —/— homozygous α-thal-1 | Tissue asphyxia, congestive heart failure, edema | Fatal in utero or at birth |

- = absent or deleted α chain; — = both genes on the locus deleted.

from bone infarctions can lead to pulmonary emboli and subsequent changes in pulmonary resistance. As the disease progresses, cor pulmonale with fatal arrhythmias can result.[3,21] In severe hemoglobinopathies, particularly thalassemia major, frequent transfusions can result in a restrictive cardiomyopathy due to iron deposition within the myocardium.[22]

**Renal.** Papillary necrosis due to chronic microinfarction of the renal papilla presents as isosthenuria—an inability to concentrate or dilute the urine, resulting in a constant altered osmolality.[23] More than half of sickle cell patients will have enlarged kidneys on radiological exam. Progressive renal destruction eventually necessitates dialysis. An association between medullary renal cell neoplasms and sickle cell disease has also been postulated.[24]

**Central nervous system** injuries can range from silent cerebral infarcts in children[16] to life-threatening major occlusion of the anterior or middle cerebral arteries in sickle cell disease. Silent strokes are the most common form of neurologic injury. Risk of stroke increases with low baseline hemoglobin, increased homocysteine levels, HLA polymorphisms, large vessel inflammation (unknown pathophysiology),[25] previous transient ischemic attacks, and priapism.[26] Occlusion can extend to the retinal vessels, resulting in hemorrhage, neovascularization (proliferative and nonproliferative retinopathy), scarring, retinal detachment, and even blindness.[27]

**Bone.** Bone, the production powerhouse of the erythrocyte, can be significantly affected in hemoglobinopathies. From early childhood, normal bone growth and development can be interrupted: medullary spaces widen as a result of chronic erythroblast hyperplasia and destruction; thinned cortices and sparse trabecular patterns can be seen;[28] vertebral bodies may show biconcavities; and a chondrolytic arthritis can develop at sites of joint space narrowing. Magnetic resonance imaging findings show extensive fibrotic scarring of the marrow cavity of long bones. Persons with thalassemia develop marked skeletal abnormalities, particularly of the skull (frontal bossing) and facial bones ("chipmunk" facies from maxillary marrow hyperplasia). In sickle cell patients, avascular necrosis of the bone commonly oc-

curs in the femoral/humeral heads; in infants under the age of 9 months, avascular necrosis can manifest as dactylitis. However, the entire skeleton is at risk of infarction; in the most dramatic presentation of bone involvement, the anterior tibia can become swollen, tender, and erythematous. Necrotic marrow presents risks of superinfection from encapsulated organisms (ie, *Salmonella* and *Staphylococcus*) and embolus to the lung, causing acute chest syndrome or sudden death.

**Reticuloendothelial system.** Increased red cell destruction in childhood leads to alterations in the reticuloendothelial system that manifest initially as splenomegaly, resultant extramedullary hematopoiesis, and eventual autosplenectomy, often between 18 and 36 months of age, with subsequent immunocompromise. Patients are particularly vulnerable to infections with encapsulated organisms.[29] Splenomegaly presents with symptoms of early satiety and laboratory values consistent with hypersplenism. In thalassemic disease, constant destruction of globin chains can lead to spleen "work hypertrophy" and a resultant hypersplenism, plasma volume expansion, and erythroid marrow expansion with worsening anemia.[3]

The destruction of dysfunctional cells in the spleen and liver can present with hepatosplenomegaly and jaundice. Between 50% and 60% of patients develop pigment gallstones, secondary to a hyperbilirubinemia; there is a low overall incidence of primary choledocholithiasis.[30] The need for recurrent transfusions in many hemoglobinopathies leads to iron overload in the liver, fibrosis, and end-stage liver disease.[31]

Acute splenic sequestration (ASSC) is a life-threatening event in the sickle cell patient. Intrasplenic trapping of red blood cells can cause a precipitous fall in hemoglobin and resultant hypovolemia. ASSC can be defined by a decrease of at least 2 g/dL from a patient's steady-state hemoglobin level with evidence of increased erythropoiesis (ie, increased reticulocyte level, enlarging spleen). Clinically, ASSC manifests with sudden weakness, pallor, tachycardia, tachypnea, and abdominal fullness.[32]

**Endocrine** abnormalities can result from hormonal and structural disruptions due to disordered hematopoiesis as well as from recurrent transfusions and subsequent iron overload. Growth retardation, growth failure, dysfunctional sexual development, diabetes and hypothyroidism are often seen.[33]

**Skin.** Ulcerations, particularly around the ankles, are common problems in sickle cell patients.[34] The general immunocompromised state of many of these patients, often exacerbated by the use of the myelosuppressive medication hydroxyurea, predisposes ulcerations to infection. In addition, lower levels of hemoglobin seen in patients with skin ulcerations (and concomitant elevations in LDH, bilirubin, and aspartate aminotransferase) suggest that hemolysis occurs at greater intensity in this patient population; transfusion provides effective therapy.[35]

## CASE CONTINUED

The patient is diagnosed with acute chest syndrome and is admitted to the hospital for further management. A comprehensive metabolic panel reveals an elevated total bilirubin of 1.7 mg/dL (normal range, 0.3–1.2 mg/dL), a direct bilirubin of 0.7 mg/dL (normal range, 0.0–0.4 mg/dL), and an LDH of 404 U/L (normal range, 94–250 U/L). The remainder of the results, including liver and renal function, are normal; coagulation parameters are within normal limits. Iron studies are not sent due to the acuity of the event; blood is sent for typing and crossmatching.

The patient receives 5 mg of morphine intravenously in the ED and is then started on a morphine patient-controlled anesthesia pump (PCA) with settings of 1 mg/hr basal rate and an as-needed bolus. A bowel regimen with docusate and senna is started to prevent narcotic-induced constipation. He also receives an intravenous (IV) infusion of ketorolac, IV fluids at 125 mL/hour, and 2 units of packed red blood cells. Empiric IV antibiotic therapy is started for possible community-acquired pneumonia. He is continued on his outpatient hydroxyurea and folate.

## MEDICAL EMERGENCIES ASSOCIATED WITH HEMOGLOBINOPATHIES

The diagnosis of a hemoglobinopathy is never an emergency. However, complications of hemoglobinopathies such as sepsis, thrombotic stroke (children), cerebral hemorrhage in adults with sickle cell anemia, rib infarction, acute chest syndrome (ACS)/acute respiratory distress syndrome, ASSC, severe aplasia, and fat embolism syndrome can all be considered emergencies.

### Pain Crises

Pain and pain crises are the most common reasons for patients with hemoglobinopathies to be hospitalized; these crises can be potent indicators of serious organ dysfunction. Four different variants of crises are differentiated: vaso-occlusive, aplastic, sequestration, and hemolytic. Vaso-occlusive crises occur most frequently; the implicated pathophysiology of such episodes includes complex interactions between endothelium, activated plasma factors, leukocytes and, in the case of sickle cell disease, rigid, inflexible red blood cells. Obstruction of the microvasculature compromises oxygen delivery to the organ. The type of vascular supply as well as the affected organ dramatically changes the acuteness of care.

### Vaso-occlusive Crises

Vaso-occlusive crises that affect the central nervous system can have devastating complications. Cerebrovascular accidents in patients with a hemoglobinopathy are thought to occur due to existent inflammatory lesions in the major vessels (ie, the internal carotid arteries and the anterior and middle cerebral arteries), with most patients have no forewarning of an imminent stroke. The highest incidence of central nervous system crises is observed in children and adults older than 29 years of age.[36] In approximately 25% of patients, prior painful or aplastic crises, transient ischemic attacks, human leukocyte antigen loci polymorphisms, low baseline hemoglobin, and an elevated diastolic blood pressure can signal a predisposition to stroke. Screening methods to identify disease before it causes extreme devastation are being investigated.[36] In particular, the use of transcranial Doppler ultrasonography in high-risk patient populations to evaluate for flow-velocity changes is showing promise. Between 46% to 90% of patients who go untreated following an initial stroke will suffer a repeat stroke; the highest percentage of repeat strokes will occur within 36 months of the initial stroke.[36] Exchange transfusion has been shown superior to simple transfusion both as acute treatment and in the prevention of a second stroke.[37] If the use of hydroxyurea in patients with prior stroke leads to a significant increase in HbF, transfusions can be discontinued.[38] In general, maintaining a HbS fraction less than 30% has also been shown to reduce the likelihood of stroke recurrence.[39]

### Acute Chest Syndrome

*Acute chest syndrome* is a general term for

any condition that results in a new pulmonary infiltrate. The differential diagnosis is pneumonia, pulmonary embolism, and primary pulmonary thrombosis. ACS clinically presents as a combination of fever, chest pain, elevated white blood count, infection, and new pulmonary infiltrates. It is thought to occur secondary to the interplay of infection, infarction, and pulmonary embolus. In a study of 538 patients with ACS, only 38% of episodes had a clear defining pathophysiologic event.[40] The incidence of ACS increases in the winter months and in children aged 2 to 4 years.[41] The concentration of HbF and degree of anemia are inversely proportional to the incidence of ACS and directly proportional to the white blood cell count.[42] Diagnostic criteria for ACS are as follows: new pulmonary infiltrate detected by chest radiograph involving at least one complete lung segment that is not consistent with the appearance of atelectasis and one or more of the following signs or symptoms:

- Chest pain
- Temperature > 38.5°C
- Tachypnea, wheezing, cough, or appearance of increased work of breathing
- Hypoxemia relative to baseline

In addition to general measures of hydration, pain control, oxygenation, and antibiotic treatment, if indicated, simple transfusion should be started and advanced to exchange transfusion or erythrocytapheresis if there is clinical progression, severe hypoxemia, multilobar disease, or previous history of severe ACS or cardiopulmonary disease. The goal of therapy is to decrease the HbS to less than 30% of total hemoglobin while not exceeding a hemoglobin level of 10 g/dL.[43]

Rib infarction can also present with a form of acute chest pain—specifically pleuritis and splinting. If not treated promptly, it can result in acute respiratory distress syndrome requiring mechanical ventilation. Aggressive analgesia and use of incentive spirometry (10 puffs every 2 hours during daytime hours) can prevent 85% of the infiltrates that develop in patients having chest pain in the hospital.[44]

**Priapism**

Low-flow priapism is a serious complication that occurs in approximately 35% of patients, usually before the age of 20 years.[45] Sickling within the venous sinusoids during erection can lead to critical stasis, hypoxia, and acidemia. If left untreated, a patient can be rendered permanently impotent. Risk factors include prolonged sexual activity; fever; dehydration; and use of alcohol, marijuana, cocaine, psychotropic agents, phosphodiesterase 5 enzyme inhibitors, or exogenous testosterone. Diagnosis is made with color duplex Doppler ultrasonography or cavernosal blood gas measurement. Neither simple nor exchange transfusion has been found beneficial in treatment of acute priapism. In erections lasting longer than 2 hours, aspiration of blood from the corpus cavernosum followed by a saline or adrenergic agonist infusion is standard treatment.[46] In severe cases, surgical procedures, such as Winter's procedure, shunt blood away from the corpus cavernosum to the more pliable corpus spongiosum.

**Thalassemia-Specific Emergencies**

Emergencies in thalassemias largely correlate with the acuity of the anemia. In β-thalassemia major, critical changes are seen in infants after 6 months of age, when hemoglobin production changes from fetal to adult hemoglobin. Infants develop chronic anemia, with stigmata of profound

hemolysis. Developmental delays, growth retardation, and abdominal swelling with enlargement of the liver and spleen, as well as consequent jaundice reflect the onset of severe hemolytic anemia. Around 80% of untreated children die within the first years of life, due to consequences of severe anemia, high-output heart failure, and susceptibility to infection.

## CASE RESOLUTION

Initially, the patient's pain does not improve, so the basal rate of his morphine PCA is increased to 2 mg/hr. Repeat blood work after 16 hours reveals a hemoglobin level of 9.2 mg/dL, with a WBC of 16,2000/μL and platelet count of 414,000/μL. The HbF level on admission is 4.7% (normal range, 0.0%–1.5%). The peripheral smear reveals an average of 2 sickled cells per high-power field, with microcytic cells and polychromasia. After 48 hours of PCA treatment, the pain medication is switched to oral oxycodone. He has no desaturation or fevers over 72 hours; his vital signs normalize and he is switched to an oral antibiotic regimen. A repeat chest radiograph reveals a decrease in the right basal opacity. After 120 hours, the patient's vital signs remain stable, he is asymptomatic, and is discharged on as-needed pain regimen and 5 more days of oral antibiotics. He is scheduled for a follow-up appointment at the Sickle Cell Hematology clinic.

## DIAGNOSIS

Diagnostic recommendations regarding the laboratory investigation of abnormal hemoglobins were first made in 1975 by the International Committee for Standardization in Hematology expert panel. The recommend initial testing included a complete blood count, electrophoresis at pH 9.2, tests for solubility, and quantification of $HbA_2$ and HbF. The identification of an abnormal hemoglobin required further testing, using additional techniques such as electrophoresis at pH 6.0 to 6.2, globin chain separation, and isoelectric focusing. Heat and isopropanol stability tests were recommended for detection of unstable hemoglobin or hemoglobin with altered oxygen affinity. Although electrophoresis at alkaline and acid pH has been widely used for many years, cation-exchange high-performance liquid chromatography, or HPLC, has become the method of choice for the quantitation of $HbA_2$ and HbF and identification of hemoglobin variants. HPLC has streamlined the recommended preliminary and follow-up tests for the identification of hemoglobinopathies, providing a rapid and complete diagnostic workup in a majority of cases. Although not usually indicated, bone marrow biopsy will demonstrate marrow erythroid hyperplasia and a prominent increase in iron. Flow cytometry is used to detect and quantify HbF. Definite diagnosis of a hemoglobin variant may require mutational analysis of a specific globin gene by polymerase chain reaction or electrophoresis gene analysis by Southern blot. Detailed structural analysis of the globin chains is done by fingerprinting of cryptic digests by electrophoresis, amino acid sequencing, and nucleic acid mutation analysis. Genetic testing is recommended in infants, as hemoglobin electrophoresis will be altered by a predominance of HbF. Genetic counseling is being used in couples with significant history to prevent severe forms of thalassemia. Extraction of fetal DNA either by amniotic fluid aspiration or chorionic villus sampling enables diagnosis of hemoglobin disorders in utero.[47] Polymerase chain reaction combined with the use of oligonucleotide probes aids in fast and reliable diagnosis of mutations.[48]

## TREATMENT

### Qualitative Hemoglobinopathies

The underlying pathophysiology of hemoglobinopathies is, with exceptions, an inherited stem cell defect. In most cases, treatment of qualitative hemoglobinopathies entails symptomatic management, whereas only a fraction of patients undergo curative-intent stem cell transplantation. Emphasis in supportive care is directed towards hydration, oxygenation, transfusion, and treatment or prevention of infection, as dehydration, low oxygen saturation, high proportion of HbS, and infection can trigger a sickle cell crisis.[49] Administration of *Haemophilus influenza* and pneumococcal vaccines is recommended, especially in children younger than 5 years. Prophylactic transfusions have been shown to decrease the frequency of vaso-occlusive crises.[50] A downside of frequent transfusions is the increased risk of developing red blood cell alloantibodies.[51] Therefore, in this patient population, it is important to transfuse leukoreduced and C, E, K1 antigen–matched blood.[52] If surgical procedures are planned, patients at risk for crises should have a HbS level lower than 30%,[49] which can be achieved through simple or exchange transfusion. Studies suggest that patients undergoing surgery with general anesthetics can be preoperatively treated with simple transfusions to hemoglobin levels of about 10 g/dL rather than with aggressive exchange transfusions.[53] The effectiveness of simple versus exchange transfusion, even in the setting of an acute vaso-occlusive crises, remains uncertain due to lack of randomized clinical trials.[54] Patients with frequent transfusions have to be monitored for iron overload syndrome and, if indicated, started on chelation therapy.[55] Folic acid supplementation is commonly used to support rapid cell regeneration, but there is little evidence of clinical benefit, except for patients who are pregnant or folate deficient.[56]

**Table 5.** Indications and Contraindications for Hydroxyurea Therapy

| Indication | Contraindication |
|---|---|
| > 3 pain crises in 1 year | Patients (female) unwilling to use contraception. |
| Persistent occurrences of priapism despite standard therapy | Receiving large numbers of narcotics regularly |
| Creatinine levels < 1.7 mg | Creatinine > 2.0 mg/dL |
| Average reticulocyte count > 150,000 | Active liver disease |
| Symptomatic anemia with alloimmunization | Positive HIV test without special informed consent |
| | Recent cerebrovascular accident |
| | History of noncompliance |

Adapted from Tamin H. Specific problems: hydroxyurea therapy. Sickle Cell Information Center. Available at: www.scinfo.org/index.php?option=com_content&view=article&id=62:specific-problems-hydroxyurea-therapy&catid=14:problem-oriented-clinical-guidelines&Itemid=27.

HbF protects red cells from sickling, although no significant correlation exists between the HbF level and the severity of clinical manifestation.[57,58] Hydroxyurea is clinically used either alone or in combination with erythropoietin to increase the amount of HbF; it has been shown to reduce the frequency of painful crises and blood transfusion and may improve overall survival.[59–61] The response to hydroxyurea is more robust in infants and children up to adolescence than in adults.[59,60] It is the only drug approved by the US Food and Drug Administration to treat sickle cell anemia. Indications and contraindications for treatment with hydroxyurea are listed in **Table 5**.[62]

The recommended dosing procedure for hydroxyurea is to administer 15 mg/kg (usually 1000 mg in adults) and check the complete blood count every 2 weeks to avoid severe leukopenia or thrombocytopenia. Every 6 weeks the dose is increased by 5 mg/kg (usually 500 mg in adults)

until the absolute neutrophil count rather than the total WBC count is approximately 1000/μL. When the patient is titered to a neutrophil count of 1000/μL, then the complete blood count can be checked every 3 months. Toxicity develops below 500/μL. Discussion of contraceptive precautions is important in patients taking hydroxyurea.

5-Azacytidine has also been found to elevate HbF levels, but it has never achieved widespread use due to concerns about carcinogenesis and toxicity. Sickle cell trait, HbC, and hemoglobin D usually have an excellent prognosis and need no specific treatment.

**Thalassemia**

Treatment for thalassemia is curative only with bone marrow transplantation. Symptomatic management for nontransplanted individuals entails blood transfusion, management of iron stores, and generalized medical care.[63,64] As in sickle cell disease, patients are at risk for infections, especially after developing skull deformities in the ENT area. Infections due to the compromised immune system should be treated empirically.[3] The skull deformities also lead to an increase in structural dental problems. Surveillance for alloimmunization and hepatitis C, hepatitis B and HIV infection should be done routinely in recipients of frequent blood transfusion. Splenectomy should only be performed in patients with sudden increased transfusion requirements or pain secondary to splenomegaly. The risk of splenectomy is susceptibility for overwhelming pneumococcal infections and thromboembolic events. Other unstable hemoglobin variants exist, and these are usually treated symptomatically with transfusion, hydration, and oxygenation. All patients with thalassemia variants that require frequent transfusion need surveillance of the iron stores and chelation therapy, if indicated. Indications for start of chelation therapy in chronic transfusion-dependent thalassemias are ferritin levels greater than 1000 mg and/or signs of iron overload.[65]

**Bone Marrow Transplantation**

Hematopoietic stem cell transplantation (HSCT) remains the only curative option for hemoglobinopathies available.[66,67] Use of HSCT in thalassemia was first described in 1982.[68] Candidates considered for transplants are usually children with poor prognosis.[52] The best results are obtained in patients with HLA-matched siblings. Hepatomegaly, hepatic fibrosis, and quality of chelation therapy have been identified as significant outcome variables in β-thalassemia transplant candidates.[69] Long-term survival after transplantation averages approximately 80%, and 85% to 90% of patients are cured.[70,71] Data on HSCT for sickle cell disease is not as extensive due to the variable course of disease and prognostic factors predicting severity of symptoms. Eligibility for transplant is limited because of advanced stage disease or missing HLA matches. The role for early transplantation in presymptomatic young children has yet to be defined. Nonmyeloablative regimens have been tried to reduce toxicity, although graft rejection or disease recurrence was seen.[72]

**Investigational Therapies**

Cell receptors and ion pump channels have been targeted to control hemolysis in sickle cell disease. Oral magnesium has been studied as an inhibitor of the KCL co-transporter, with insufficient data supporting a benefit. Anti-adherence therapy targeting erythrocyte-endothelial-leukocytes and platelets has been studied without any current clinical approved therapies. Nitric oxide, a potent vasodilator, has been used in the treatment of

acute sickle cell disease and found to reduce the pain score and pain medication use in children.[73]

In thalassemia, peripheral stem cell transplant as opposed to HSCT has been studied. Compared to bone marrow transplantation, it has a shorter engraftment time but a higher incidence of graft-versus-host disease.[74] In view of the low incidence of graft-versus-host disease associated with allogenic cord blood transplantation (CBT), this procedure is particularly appealing. Available evidence indicates that related donor CBT is a safe and effective option for patients with hemoglobinopathies, offering results at least as good as those reported using bone marrow cells.[75] Hematopoietic stem cell–targeted gene transfer is currently being investigated as a treatment option for hemoglobinopathies caused by single gene defects.[76]

### OUTCOMES AND PROGNOSIS

Transfusion and chelation treatment have improved outcomes in severe forms of β-thalassemia. Patients with an estimated serum ferritin level below 500 ng/mL over a period of 12 years were found to have a disease-free survival rate of 91%.[77] Transplantation is able to cure patients and has become a standard procedure. In milder forms of thalassemia, judicious use of splenectomy in patients with hypersplenism, vaccination, and a good standard of general care have an impact on survival. Prevention through screening and genetic counseling remains essential to prevent severe forms of thalassemia.

Survival in sickle cell disease patients is overall reduced but has been steadily improving. With good medical care, patients with sickle cell disease survive to middle age.[77] Over the last few decades, mortality has especially dropped in children. Survival has improved due to newborn screening programs, penicillin prophylaxis of disease caused by *Streptococcus pneumoniae*, and perhaps pneumococcal vaccine. The most common cause of death in sickle cell disease is infection, and others are pulmonary emboli, stroke, and splenic sequestration. Neither sickle cell trait nor HbC appear to impact survival. Genetic counseling also is important to prevent severe disease and disease side effects. Patients at high risk for sickle cell disease have the option of transplantation.

## CONCLUSION

Hemoglobinopathies are hemopoietic stem cell disorders with qualitative, quantitative, and combined globin chain abnormalities. The range of newly diagnosed genotypes with resulting phenotype has been steadily increasing due to improved laboratory diagnostic procedures. Treatment remains supportive in the majority of encountered diseases. Curative treatment in high-risk patients is limited to HSCT. Transplantation has significant risks but has become standard procedure, more so in thalassemias than in sickle cell disease, due to improved peri- and posttransplantation care. Genetic counseling and screening are relevant in predicting and diagnosing clinical significant genotypes. Further studies are needed to expedite curative treatment options and prevent recurrent crises and long-term side effects.

**BOARD REVIEW QUESTIONS**

**Test your knowledge of this topic. Go to www.turner-white.com and select Hematology from the drop-down menu of specialties.**

## REFERENCES


1. Clarke GM, Higgins TN. Laboratory investigation of hemoglobinopathies and thalassemias: review and update. Clin Chem 2000;46(8 Pt 2):1284–90.
2. Chotivanich K, Udomsangpetch R, Pattanapanyasat K, et al. Hemoglobin E: a balanced polymorphism protective against high parasitemias and thus severe P falciparum malaria. Blood 2002;100:1172–6.
3. Lichtman M, Beutler E, Kaushansky E, et al. Williams hematology. 7th ed. New York: McGraw-Hill Companies; 2005.
4. Oo M, Tin-Shwe, Marlar-Than, O'Sullivan WJ. Genetic red cell disorders and severity of falciparum malaria in Myanmar. Bull World Health Organ 1995;73:659–65.
5. Fairhurst RM, Fujioka H, Hayton K, et al. Aberrant development of *Plasmodium falciparum* in hemoglobin CC red cells: implications for the malaria protective effect of the homozygous state. Blood 2003;101:3309–15.
6. Allen SJ, O'Donnell A, Alexander ND, et al. Alpha+-Thalassemia protects children against disease caused by other infections as well as malaria. Proc Natl Acad Sci USA 1997;94:14736–41.
7. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ 2001;79:704.
8. Benz EJ. Disorders of hemoglobin. In: Fauci AS, Kasper DL, Hauser SL, et al, editors. Harrison's principles of internal medicine. New York: McGraw-Hill Companies; 2007.
9. Kjeldsberg C. Practical diagnosis of hematologic disorders. Chicago: ASCP Press; 2006.
10. Pagnier J, Mears JG, Dunda-Belkhodja O, et al. Evidence for the multicentric origin of the sickle cell hemoglobin gene in Africa. Proc Natl Acad Sci USA 1984;81:1771–3.
11. Flatz G. Hemoglobin E: distribution and population dynamics. Humangenetik 1967;3:189–234.
12. Angastiniotis M, Modell B. Global epidemiology of hemoglobin disorders. Ann N Y Acad Sci 1988;850:251–69.
13. Alexy T, Sangkatumvong S, Connes P, et al. Sickle cell disease: selected aspects of pathophysiology. Clin Hemorheol Microcirc 2010;44:155–66.
14. Serjeant GR, Serjeant BE, Milner PF. The irreversibly sickled cell; a determinant of haemolysis in sickle cell anaemia. Br J Haematol 1969;17:527–33.
15. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994;330:1639–44.
16. Buchanan GR, DeBaun MR, Quinn CT, Steinberg MH. Sickle cell disease. Hematology Am Soc Hematol Educ Program 2004:35–47.
17. Miller GJ, Serjeant GR, Sivapragasam S, Petch MC. Cardio-pulmonary responses and gas exchange during exercise in adults with homozygous sickle-cell disease (sickle-cell anaemia). Clin Sci 1973;44:113–28.
18. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004;350:886–95.
19. Vichinsky EP. Pulmonary hypertension in sickle cell disease. N Engl J Med 2004;350:857–9.
20. Ardiles T, Dark D. Pulmonary complications of sickle cell disease in adults. Mo Med 2007;104:250–4.
21. Castro O. Systemic fat embolism and pulmonary hypertension in sickle cell disease. Hematol Oncol Clin North Am 1996;10:1289–303.
22. Tsironi M, Polonifi K, Deftereos S, et al. Transfusional hemosiderosis and combined chelation therapy in sickle thalassemia. Eur J Haematol 2005;75:355–8.
23. Maigne G, Ferlicot S, Galacteros F, et al. Glomerular lesions in patients with sickle cell disease. Medicine (Baltimore) 2010;89:18–27.
24. Baron BW, Mick R, Baron JM. Hematuria in sickle cell anemia—not always benign: evidence for excess frequency of sickle cell anemia in African Americans with renal cell carcinoma. Acta Haematol 1994;92:119–22.
25. Verduzco LA, Nathan DG. Sickle cell disease and stroke. Blood 2009;114:5117–25.
26. Adams RJ, Ohene-Frempong K, Wang W. Sickle cell and the brain. Hematology Am Soc Hematol Educ Program 2001:31–46.
27. Fadugbagbe AO, Gurgel RQ, Mendonca CQ, et al. Ocular manifestations of sickle cell disease. Ann Trop Paediatr 2010;30:19–26.
28. Vichinsky EP. The morbidity of bone disease in thalassemia. Ann N Y Acad Sci 1998;850:344–8.
29. Boghossian SH, Wright G, Webster AD, Segal AW. Investigations of host defence in patients with sickle cell disease. Br J Haematol 1985;59:523–31.
30. Vicari P, Gil MV, Cavalheiro Rde C, Figueiredo MS. Multiple primary choledocholithiasis in sickle cell disease. Intern Med 2008;47:2169–70.
31. Ebert EC, Nagar M, Hagspiel KD. Gastrointestinal and hepatic complications of sickle cell disease. Clin Gastroenterol Hepatol 2010;8:483–9.
32. Wang WC. Splenic sequestration and transient aplastic crises. 2000. Available at: http://sickle.bwh.harvard.edu/spleen.html.
33. Fung EB, Harmatz P, Milet M, et al. Morbidity and mortality in chronically transfused subjects with thalassemia and sickle cell disease: a report from the multi-center study of iron overload. Am J Hematol 2007;82:255–65.
34. Serjeant GR, Serjeant BE, Mohan JS, Clare A. Leg ulceration in sickle cell disease: medieval medicine in a modern

world. Hematol Oncol Clin North Am 2005;19:943–56, viii-ix.
35. Nolan VG, Adewoye A, Baldwin C, et al. Sickle cell leg ulcers: associations with haemolysis and SNPs in Klotho, TEK and genes of the TGF-beta/BMP pathway. Br J Haematol 2006;133:570–8.
36. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998;91:288–94.
37. Hulbert ML, Scothorn DJ, Panepinto J, et al. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. J Pediatr 2006;149:710–2.
38. Ware RE, Zimmerman SA, Schultz WH. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. Blood 1999;94:3022–6.
39. Williams J, Goff JR. Efficacy of transfusion therapy for one to two years in patients with sickle cell disease and cerebrovascular accidents. J Pediatr 1980;96:205–8.
40. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med 2000;342:1855–65.
41. Castro O, Brambilla DJ, Thorington B, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood 1994;84:643–9.
42. Graham LM. Sickle cell disease: pulmonary management options. Pediatr Pulmonol Suppl 2004;26:191–3.
43. Telen MJ. Principles and problems of transfusion in sickle cell disease. Semin Hematol 2001;38:315–23.
44. Bellet PS, Kalinyak KA, Shukla R, et al. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. N Engl J Med 1995;333:699–703.
45. Mantadakis E, Cavender JD, Rogers ZR, et al. Prevalence of priapism in children and adolescents with sickle cell anemia. J Pediatr Hematol Oncol 1999;21:518–22.
46. Rogers ZR. Priapism in sickle cell disease. Hematol Oncol Clin North Am 2005;19:917–28, viii.
47. Old JM, Fitches A, Heath C, et al. First-trimester fetal diagnosis for haemoglobinopathies: report on 200 cases. Lancet 1986;2:763–7.
48. Saiki RK, Chang CA, Levenson CH, et al. Diagnosis of sickle cell anemia and beta-thalassemia with enzymatically amplified DNA and nonradioactive allele-specific oligonucleotide probes. N Engl J Med 1988;319:537–41.
49. Shah A. Hemoglobinopathies and other congenital hemolytic anemia. Indian J Med Sci 2004;58:490–3.
50. Laulan S, Bernard JF, Boivin P. Systematic blood transfusions in adult homozygote sickle-cell anemia. Study of 11 cases followed for 5 to 10 years. Presse Med 1990;19:785–9.
51. Rosse WF, Gallagher D, Kinney TR, et al. Transfusion and alloimmunization in sickle cell disease. The Cooperative Study of Sickle Cell Disease. Blood 1990;76:1431–7.
52. Roseff SD. Sickle cell disease: a review. Immunohematology 2009;25:67–74.
53. Vichinsky EP, Haberkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group. N Engl J Med 1995;333:206–13.
54. Alhashimi D, Fedorowicz Z, Alhashimi F, Dastgiri S. Blood transfusions for treating acute chest syndrome in people with sickle cell disease. Cochrane Database Syst Rev 2010(1):CD007843.
55. Silliman CC, Peterson VM, Mellman DL, et al. Iron chelation by deferoxamine in sickle cell patients with severe transfusion-induced hemosiderosis: a randomized, double-blind study of the dose-response relationship. J Lab Clin Med 1993;122:48–54.
56. Dhar M, Bellevue R, Carmel R. Pernicious anemia with neuropsychiatric dysfunction in a patient with sickle cell anemia treated with folate supplementation. N Engl J Med 2003;348:2204–7.
57. Noguchi CT, Rodgers GP, Serjeant G, Schechter AN. Levels of fetal hemoglobin necessary for treatment of sickle cell disease. N Engl J Med 1988;318:96–9.
58. Powars DR, Schroeder WA, Weiss JN, et al. Lack of influence of fetal hemoglobin levels or erythrocyte indices on the severity of sickle cell anemia. J Clin Invest 1980;65:732–40.
59. Rodgers GP, Dover GJ, Uyesaka N, et al. Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle cell disease. N Engl J Med 1993;328:73–80.
60. Davies SC, Gilmore A. The role of hydroxyurea in the management of sickle cell disease. Blood Rev 2003;17:99–109.
61. Zimmerman SA, Schultz WH, Davis JS, et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood 2004;103:2039–45.
62. Steinberg MH. Management of sickle cell disease. N Engl J Med 1999;340:1021–30.
63. Cao A, Galanello R. Beta-thalassemia. Genet Med 2010;12:61–76.
64. Weatherall DJ, Clegg JB. The thalassemia syndromes. 4th ed. Oxford (UK): Blackwell Science; 2001.
65. Taher A, Hershko C, Cappellini MD. Iron overload in

thalassaemia intermedia: reassessment of iron chelation strategies. Br J Haematol 2009;147:634–40.
66. Smiers FJ, Krishnamurti L, Lucarelli G. Hematopoietic stem cell transplantation for hemoglobinopathies: current practice and emerging trends. Pediatr Clin North Am 2010;57:181–205.
67. Hsieh MM, Kang EM, Fitzhugh CD, et al. Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. N Engl J Med 2009;361:2309–17.
68. Thomas ED, Buckner CD, Sanders JE, et al. Marrow transplantation for thalassaemia. Lancet 1982;2:227–9.
69. Lucarelli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in thalassemia. Hematol Oncol Clin North Am 1991;5:549–56.
70. Boulad F, Giardina P, Gillio A, et al. Bone marrow transplantation for homozygous beta-thalassemia. The Memorial Sloan-Kettering Cancer Center experience. Ann N Y Acad Sci 1998;850:498–502.
71. Lawson SE, Roberts IA, Amrolia P, et al. Bone marrow transplantation for beta-thalassaemia major: the UK experience in two paediatric centres. Br J Haematol 2003;120:289–95.
72. Michlitsch JG, Walters MC. Recent advances in bone marrow transplantation in hemoglobinopathies. Curr Mol Med 2008;8:675–89.
73. Sullivan KJ, Goodwin SR, Evangelist J, et al. Nitric oxide successfully used to treat acute chest syndrome of sickle cell disease in a young adolescent. Crit Care Med 1999;27:2563–8.
74. Iravani M, Tavakoli E, Babaie MH, et al. Comparison of peripheral blood stem cell transplant with bone marrow transplant in class 3 thalassemic patients. Exp Clin Transplant 2010;8:66–73.
75. Boncimino A, Bertaina A, Locatelli F. Cord blood transplantation in patients with hemoglobinopathies. Transfus Apher Sci 2010;42:277–81.
76. Persons DA. Hematopoietic stem cell gene transfer for the treatment of hemoglobin disorders. Hematology Am Soc Hematol Educ Program 2009:690–7.
77. Olivieri NF, Nathan DG, MacMillan JH, et al. Survival in medically treated patients with homozygous beta-thalassemia. N Engl J Med 1994;331:574–8.